

ABSTRACT

Title of Document: TANDEM REDUCTION/CYCLIZATION OF O-NITROPHENYL PROPARGYL ALCOHOLS—A NOVEL SYNTHESIS OF 2- & 2,4-DISUBSTITUTED QUINOLINES AND APPLICATION TO THE SYNTHESIS OF STREPTONIGRIN

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The quinoline ring system is a common structural component of a wide variety of natural products with highly desirable biological activity, including antimalarial agents such as quinine, chloroquine and mefloquine, as well as antitumor agents such as dynemicin A, luotonin A, and camptothecin. The synthesis of the highly effective, yet prohibitively toxic, antitumor antibiotic streptonigrin is targeted in this research. A concise, convergent synthesis of this antitumor agent will pave the way for an expeditious survey of streptonigrin analogues that have similar pharmaceutical value with diminished toxicity. Our retrosynthetic plan required the development of new methodology to form the heterocyclic ring of quinoline, in a manner that would allow the utilization of palladium-catalyzed coupling of complex aryl triflates to form the tetracyclic structure of this highly functionalized natural product.

A method has been developed to synthesize complex, substituted quinolines in a facile manner through the utilization of *o*-nitrophenyl propargyl alcohols. Through either direct lithium acetylide addition of available alkynes, or Sonogashira coupling to terminal propargyl alcohols, the assembly of complex internal propargyl alcohols has directly lead to 2-aryl-, 2-alkenyl and 2-alkylquinolines via reductive cyclization under mildly acid conditions. This reductive cyclization takes advantage of the facile Meyer-Schuster rearrangement of resonance-stabilized *o*-anilinopropargyl alcohols to *o*-aminochalcones, which cyclize to quinoline in a one-pot procedure.

This work has also examined the use of this reductive cyclization to form 2-pyridylquinolines, however such cyclization has repeatedly led to the 4-quinolone. The mechanism of such an anomalous cyclization has been studied. Although the mechanism has not been definitively identified, several potential pathways have been examined, with evidence favoring an acid-catalyzed, non-Meyer-Schuster rearrangement of the propargyl alcohol leading to cyclization and oxidative rearomatization to form the observed quinolone.

Lastly, reductive cyclization has been applied to model systems for the ABC-ring system of the natural product streptonigrin. The synthesis of an appropriate A-ring precursor *o*-mononitrobenzaldehyde has been achieved, and elaborated to the final 6,8-dimethoxy-2-(2'-pyridyl)quinolone through reductive cyclization. A more intriguing A-ring precursor dinitrobenzaldehyde, with built-in functionality to produce streptonigrin's 7-amino group, was also targeted. Efforts toward its regioselective synthesis are also described.

TANDEM REDUCTION/CYCLIZATION OF O-NITROPHENYL PROPARGYL
ALCOHOLS—A NOVEL SYNTHESIS OF 2- & 2,4-DISUBSTITUTED
QUINOLINES AND APPLICATION TO THE SYNTHESIS OF STREPTONIGRIN

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These short words could never begin to describe the support I have received from my wife. Her strength to bear the countless lonely dinners and those sunny Saturday afternoons not spent in the park paled only by her uplifting smile as I walked through the door, stressed and exhausted from that day's test. Each and every day she bolstered my spirits, always treating me like the smartest guy she knows--clearly she doesn't know many people.

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List of Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
AcOH	acetic acid
Ar	aryl
ATP	adenosine-5'-triphosphate
Bn	benzyl
BOC	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
calcd	calculated
conc	concentrated
Cy	cyclohexyl
d	day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
decomp	decomposition
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
EDG	electron-donating group
EI	electron ionization
eq	equivalent(s)
Et	ethyl
EWG	electron-withdrawing group
FAB	fast-atom bombardment
<i>gem</i>	geminal

h	hour(s)
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
Hz	Hertz
<i>J</i>	coupling constant
L	ligand
LCMS	liquid chromatography-mass spectrometry
<i>m</i>	<i>meta</i>
<i>m/z</i>	mass to charge ratio
Me	methyl
min	minute(s)
mp	melting point
MOM	methoxymethyl
MS	mass spectrometry
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NBS	<i>N</i> -bromosuccinimide
NMO	<i>N</i> -Methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
Nuc	nucleophile
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Ph	phenyl
PhAc	acetophenone
Piv	pivaloyl
PMB	<i>para</i> -methoxybenzyl
PPA	polyphosphoric acid
pTSA	<i>p</i> -toluenesulfonic acid
Py	pyridine
TBAF	tetrabutylammonium fluoride

TBAT.....	tetrabutylammonium triphenyldifluorosilicate
TBS.....	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>tert</i> -butyl
TEA	triethylamine
Tf	trifluoromethane sulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS.....	triisopropylsilyl
TLC.....	thin-layer chromatography
TMEDA.....	<i>N,N,N',N'</i> -tetramethylenediamine
Ts	tosyl

Introduction

This manuscript details progress in the DeShong research group toward the total synthesis of the antitumor, antibiotic natural product streptonigrin (**1**) (Figure 1). Previous work in the DeShong group conducted by Dr. William McElroy produced a late stage CD ring pyridyl triflate intermediate (**2**),^{1,2} that incorporated the functionality of the natural product. In order to complete the synthesis of streptonigrin from intermediate **2** in a convergent and efficient manner, we have developed a new synthetic route to 2-arylquinolines, similar to the structure of the AB ring system of streptonigrin. Although this heteroannulation of quinoline was developed specifically to apply to the synthesis of streptonigrin, the methodology can be utilized for the synthesis of a wide variety of 2- and 2,4-substituted quinolines, particularly in cases where complex aryl substituents are required at the 2-position of quinoline.

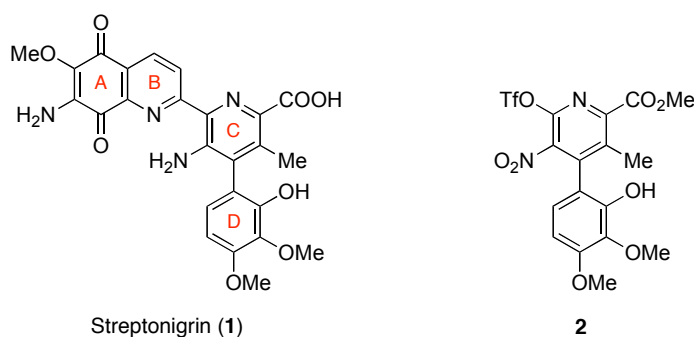


Figure 1. Streptonigrin (**1**) and McElroy's Intermediate (**2**)

The following introductory material will survey the wealth of research directed toward the synthesis of quinolines, including century-old named reactions and their

more recent modifications that have dominated quinoline research, placing this new work into the context of those past syntheses. Also, a vital component of our proposed mechanism for this synthesis utilizes the facile rearrangement of propargyl alcohols to α,β -unsaturated enones--the Meyer-Schuster rearrangement. Therefore, a short review of the history, mechanistic studies and applications of that rearrangement is provided. Lastly, the significance of a new synthetic route to streptonigrin is established through a summary of both its pharmaceutical value and the few elegant, yet lengthy, past total syntheses of this important natural product.

Heteroannulation – Formation of Quinolines

The quinoline ring system has been heavily studied as a synthetic target since its discovery by Gerhardt in 1842.³ Although some synthetic work has been directed toward organic materials and dyes, the lion's share of quinoline research has been focused on pharmaceuticals. A few of the major targets have included treatments for parasitic infections such as malaria and leishmaniasis, as well as antitumor agents such as streptonigrin (**1**),^{4,5} dynemicin A (**2**),^{6,7} luotonin A (**3**),⁸ and camptothecin (**4**)⁹ (Figure 2). Along with those formidable targets, natural product isolations and biological activity assays continue to identify new, potentially useful quinoline alkaloids from both plant and marine animal sources each year.¹⁰⁻²⁰

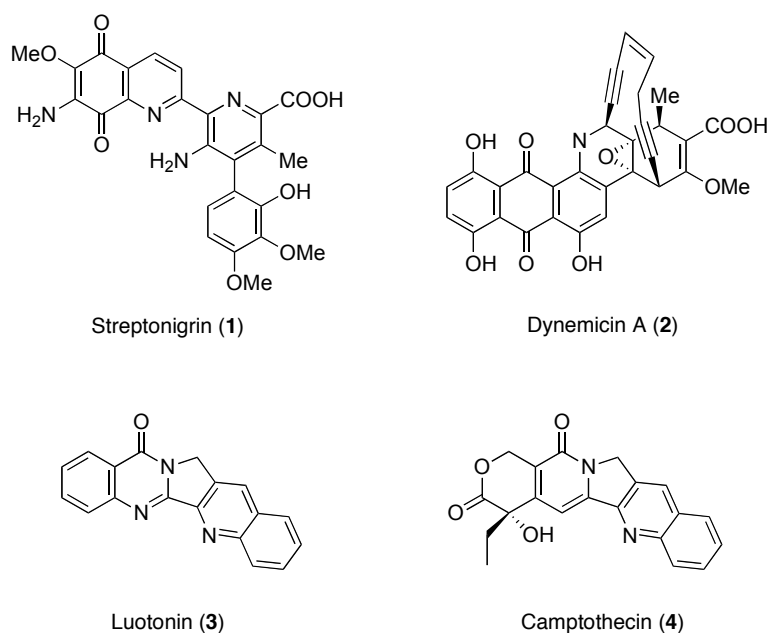


Figure 2. Quinoline-based Natural Product Targets

The early work on quinolines was clearly guided toward the fight against malaria—a fight that still rages today. Despite centuries of work on quinine (**5**), its asymmetric synthesis was only recently achieved by Stork.²¹ Stork's process did not represent a novel quinoline ring synthesis—he used 6-methoxy-4-methylquinoline as a starting material. However, the longtime goal of a stereospecific quinine synthesis highlights the continued need for quinoline-based antimalarial agents. According to the World Health Organization, malaria's annual death toll is estimated at 1-3 million people, mostly in young sub-Saharan African children. Treatments have focused on a class of aryl aminoalcohols, including quinine (**5**), quinidine (**6**), mefloquine (**7**), chloroquine (**9**), amodiaquine (**10**), and piperazine (**11**)²² (Figure 3).

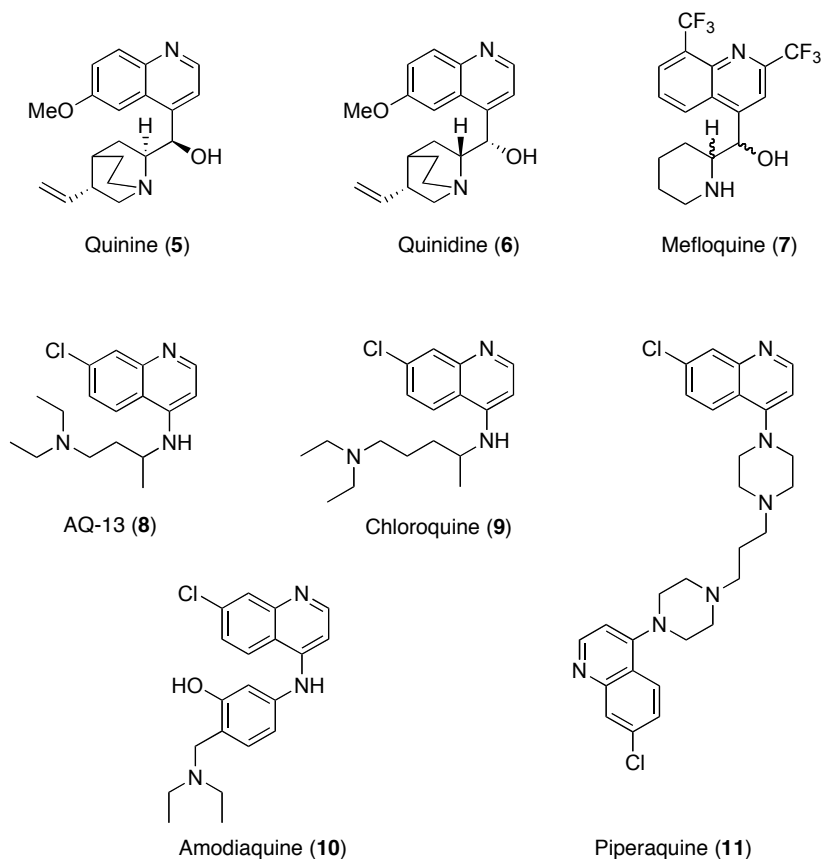


Figure 3. Quinoline-based Antimalarial Chemotherapeutic Agents

The synthesis of new quinolines has played a critical role this fight. Various substituted quinolines have been developed over the years to treat *Plasmodium falciparum*, the most virulent protozoa involved in the spread of malaria. However, *P. falciparum* has proven itself formidable, growing resistance to each new treatment. The first such treatment, quinine (**5**), was introduced in the 19th century but resistance was found in 1910. Chloroquine (**9**), brought into the fight in 1945, was effective for a time but in 1957 chloroquine-resistant strains were discovered. In the late 1970s, subsequent screening for effective analogues of chloroquine identified mefloquine (**7**). But yet again, mefloquine-resistant strains were quickly identified. Recently, a new aminoquinoline AQ-13 (**8**), has been screened as a potent agent in otherwise resistant strains of *P. falciparum*.²³ This new quinoline target will be used in conjunction with a newer class of antimalarial agents, derived from the non-quinoline-based natural product artemisinin. This combination therapy is hoped to be effective against resistant strains of *P. falciparum*.

Excellent reviews of the synthesis of quinoline systems have been written as early as 1942, by R. Manske,³ and as recently as 2005 by Kouznetsov.²⁴ For the sake of brevity, this review will not attempt to thoroughly cover the enormous volume of work on synthesizing quinolines in the past 150 years. This summary will survey the recent work done in the field, focusing on new techniques to generate quinoline's heterocyclic ring, referencing the classical syntheses only when necessary to set the tone of the current work.

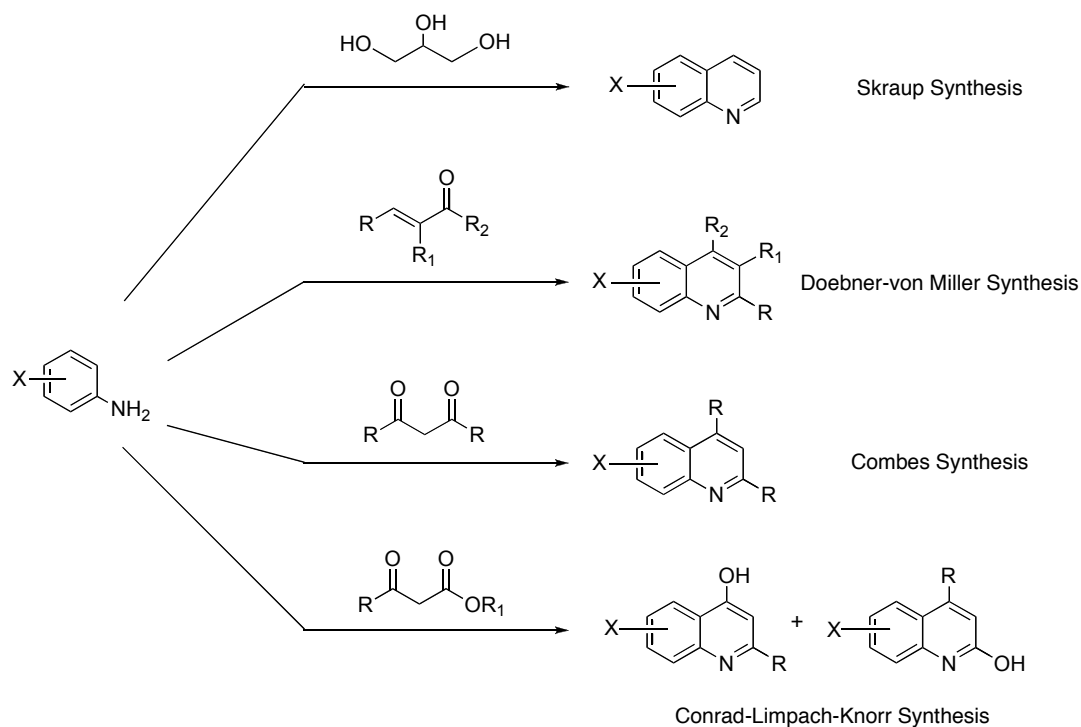
In order to categorize each of the new quinoline synthesis techniques, it is necessary to compare them to the body of classical methods. To date, there is a

wealth of named reactions used to generate the quinoline ring system. Those named reactions can be broken down into two classes based on the substitution pattern of the starting materials.²⁴ Those that begin with unsubstituted anilines include the Skraup, Doebner-von Miller, Conrad-Limpach-Knorr, and Combes syntheses. Those that begin with *ortho*-substituted anilines include the Friedländer, Pfitzinger, Niemantowski and Borsche syntheses. Although each technique has its own set of advantages and limitations, the Skraup and Friedländer work set the baseline for all other variations.

SKRAUP AND SKRAUP-LIKE TECHNIQUES

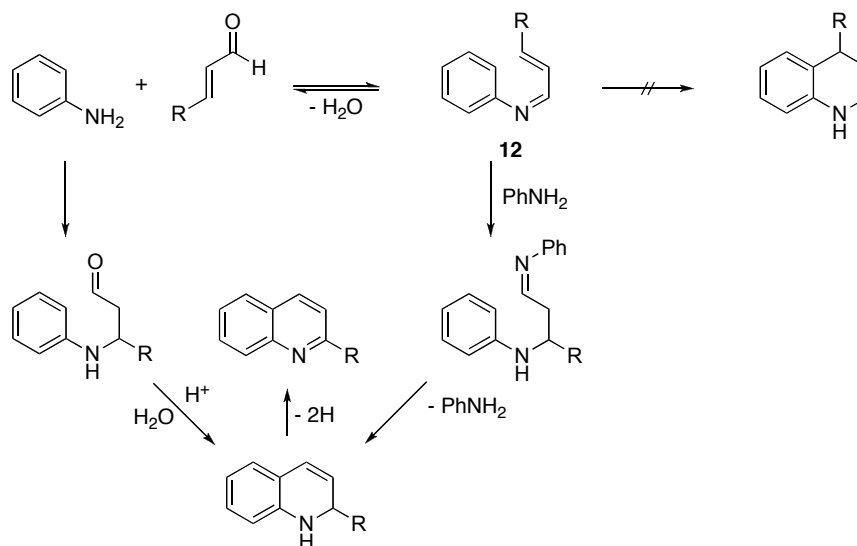
The Skraup, Doebner-von Miller, Conrad-Limpach-Knorr and Combes syntheses each start with aniline as the nucleophilic nitrogen component, and vary in the additional electrophilic 3-carbon piece added (Scheme 1). In the Skraup synthesis,²⁵ aniline was heated with glycerin, sulfuric acid and an oxidizing agent, such as nitrobenzene, to form quinoline. Doebner and von Miller²⁶ substituted 1,2-glycols or α,β -unsaturated aldehydes for the glycerine, to condense with the aniline to form the same pyridinoid ring. The Conrad-Limpach-Knorr reaction used acetoacetic esters,^{27,28} and the Combes method²⁹ involved heating aniline with acetylacetone.

Scheme 1



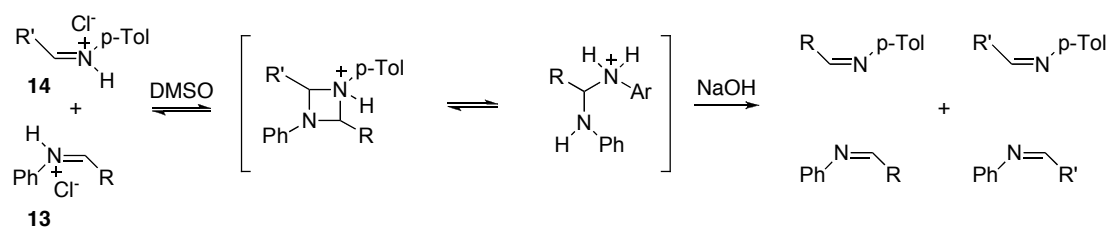
The mechanism of the Skraup/Doebner von Miller syntheses was quite controversial. Skraup's proposed mechanism was based on producing Schiff base intermediate **12** (Scheme 2), which directly cyclized with the aromatic ring. However, this could not explain the regiochemistry found using α,β -unsaturated aldehydes, which led exclusively to 2-substituted quinolines.³⁰ In 1892, Bischler proposed a mechanism that involved the 1,4-addition of aniline with Skraup's Schiff base, which after elimination formed the observed 2-substituted quinoline.³¹

Scheme 2



Eisch's work used the hydrochlorides of cinnamaldehyde anil (**13**) and *N*-(*p*-methylcinnamylidene)-*p*-toluidine (**14**), under strictly anhydrous conditions, and observed an exchange reaction, leading to a mixture of four Schiff bases (Scheme 3).

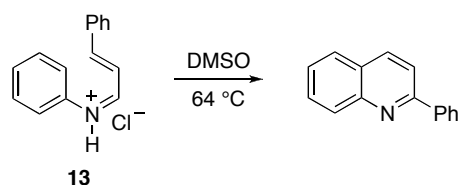
Scheme 3



Eisch also measured the rate of disappearance of cinnamaldehyde anil hydrochloride **13** (Scheme 4) over timed intervals at a controlled temperature.

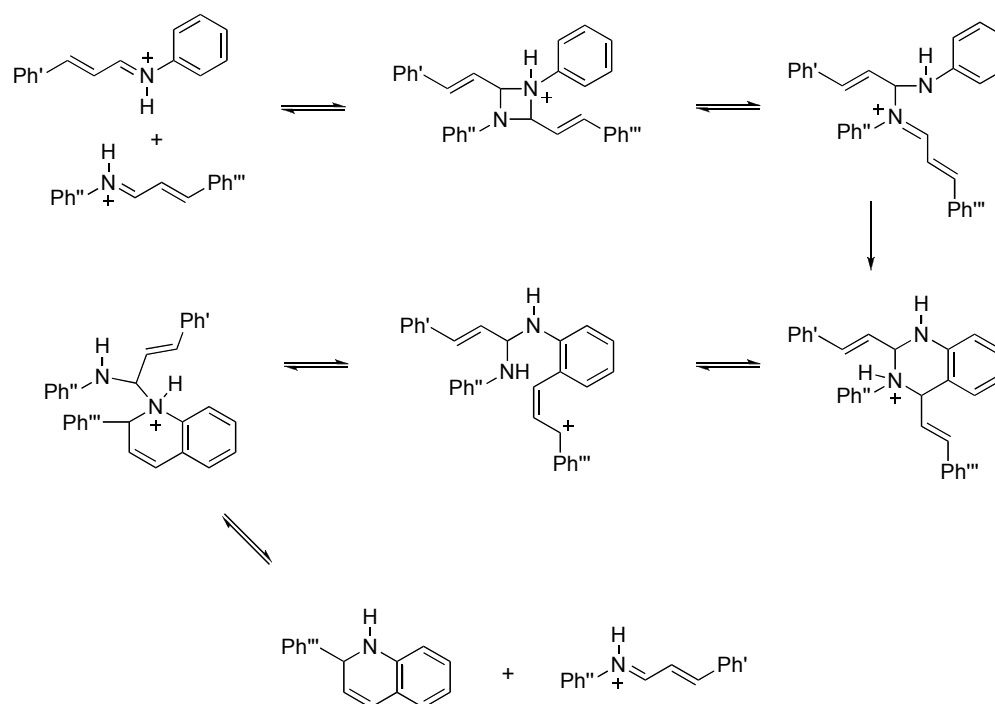
Regression analysis of that data best fit a first-order dependence on the concentration of **13**.

Scheme 4



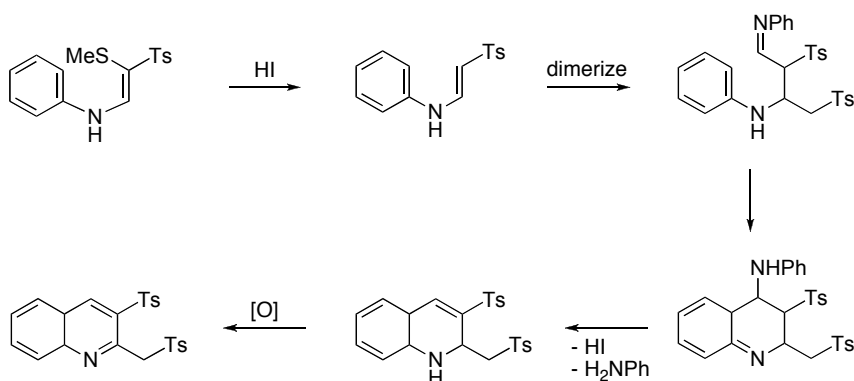
Combining these observations, Eisch proposed a diazetidininium cation intermediate (Scheme 5). This proposal agreed with his first-order kinetic data, since the second molecule of anil is regenerated in the process. This proposed mechanism also explained the observed regiochemistry of generating 2-phenylquinoline, with no observed 4-phenylquinoline.³⁰

Scheme 5



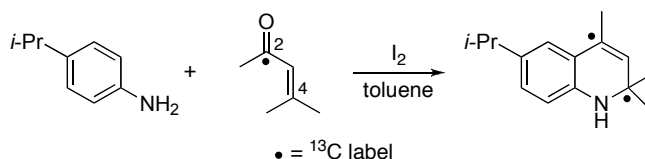
A recent study reported by Matsumoto and Ogura³² followed a similar mechanistic pathway. Tosylenamines, formed *in situ* by the hydrogen iodide reduction of 2-(arylamino)-1-(methylthio)1-tosylethenes, dimerize to form an imine capable of electrophilic ring closure, which after aniline elimination and oxidation, formed 3-tosyl-2-(tosylmethyl)quinolines in good yield (Scheme 6).

Scheme 6



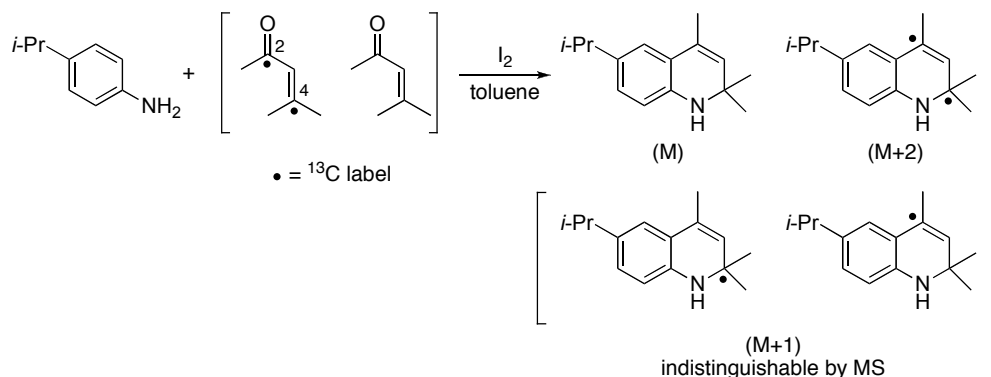
In an attempt to further elucidate the mechanism of the Skraup/Doebner von Miller quinoline synthesis, Denmark conducted a series of isotopic labeling experiments cyclizing *p*-isopropylaniline with mesityl oxide ¹³C-labeled once at the 2-position or labeled at both 2- and 4-positions.³³ The ¹³C(2)-mesityl oxide experiment led to a quinoline product with ¹³C-enrichment at both possible positions (Scheme 7).

Scheme 7



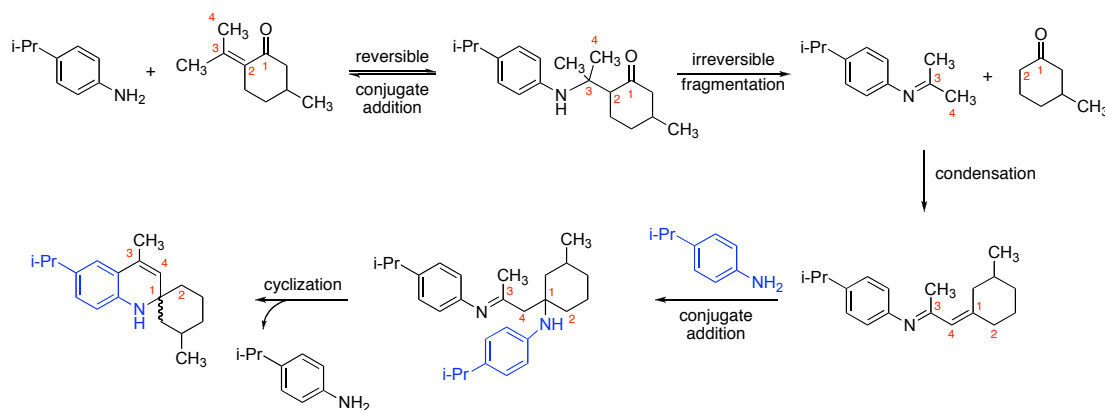
This result implied that either (1) multiple mechanistic pathways were simultaneously operative, leading to a mixture of labeled quinoline products, (2) the mesityl oxide acetone subunits were scrambling during the cyclization, or (3) mesityl oxide was scrambling prior to and separate from the cyclization process. Control experiments led Denmark to conclude that the impact of mesityl oxide scrambling outside of the cyclization process (option 3) was minimal. Denmark next ran crossover cyclizations using a mixture of $^{13}\text{C}(2,4)$ -labeled mesityl oxide and mesityl oxide at natural abundance (Scheme 8). In those reactions, the mass distribution of quinoline was enriched in singly labeled $(M+1)^+$ product equal to the extent theoretically expected by random scrambling. Since the retro aldol/aldol scrambling of mesityl oxide itself was previously excluded, Denmark concluded that the acetone units of mesityl oxide were separating and recombining *during* the cyclization process.

Scheme 8



Further studies by Denmark with a different α,β -unsaturated ketone led to the same basic conclusion--although a definitive mechanism was not clearly established, Denmark believed the Skraup reaction occurs through a sequence of (1) conjugate addition of the aniline to the enone, (2) fragmentation/recombination of the ketone segment leading to a new Schiff base, (3) conjugate addition of a second aniline molecule, and (4) cyclization and elimination of the first aniline to form quinoline. Not unlike Eisch's rationalization, this proposed mechanistic sequence explained the observed regiochemistry of the resulting quinolines produced by the Skraup/Doebner von Miller reaction, while adhering to the scrambling observed in Denmark's isotopic labeling experiments.

Scheme 9



Recent applications of the Skraup reaction highlight its utility. In 2000, Boger used a modified Skraup reaction using bromoacrolein in his synthesis of an analogue of duocarmycin A, an active antitumor antibiotic.³⁴ In 2003, Heinrich used acrolein

in an acidic solution with a 3-aminocatechol to form the quinoline-7,8-diols needed in the total synthesis of the marine alkaloid halitulin (**15**) (Figure 4).³⁵

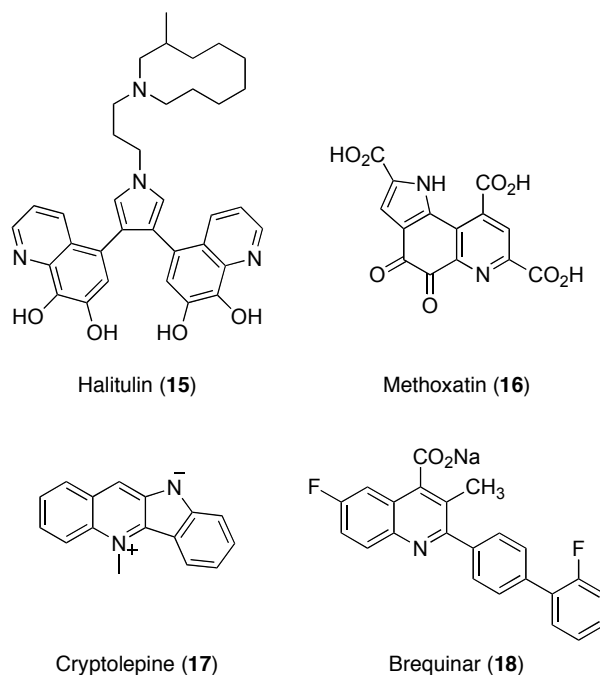
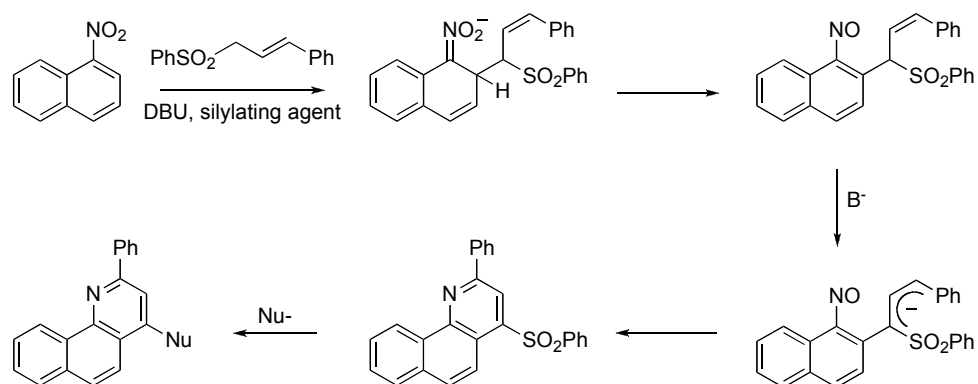


Figure 4. More Quinoline-based Natural Product Targets

The harsh conditions required for these reactions—high temperatures and highly acidic medium—have prompted considerable work in modifying the procedure to find more mild, yet regiospecific conditions. In 2002, Theoclitou and coworkers used microwaves to shorten the times of Skraup reactions from 60 hours down to 1 hour with similar yields. Since this improvement was not sufficient for their goal of developing a combinatorial Skraup synthesis, they also developed a route using scandium triflate catalysis. This improved the yield significantly, and along with the microwave assistance, produced the desired Skraup reaction products at room temperature, in an expedient manner.³⁶

In 1998, Wrobel developed a quinoline synthesis analogous to the Skraup synthesis, switching the polarity of the two components. He used nitroarenes as an electrophilic nitrogen source, and cinnamyl phenyl sulfone, which under mildly basic conditions, formed a nucleophilic three-carbon unit. This procedure formed 2-phenyl-4-phenylsulfonyl-quinolines which could be treated with various nucleophiles to undergo S_NAr reactions with the phenyl sulfone to generate 2-arylquinolines with a variety of 4-substituents (Scheme 10).³⁷

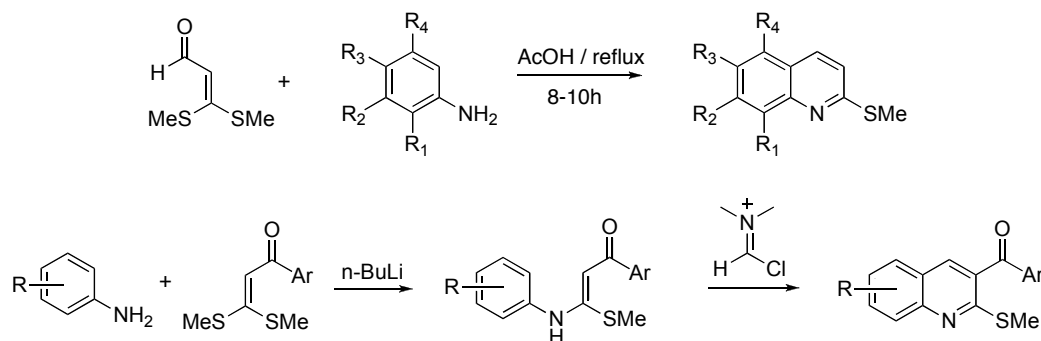
Scheme 10



Ila and coworkers developed a modified Skraup synthesis using 3-bis(methylthio)acrolein as a “surrogate” acrolein, which was synthesized from vinyl acetate (Scheme 11, upper equation)³¹. This mild method was an improvement over their previous work which used a similar α -oxoketene-*N,S*-anilinoacetal in a regioselective synthesis of functionalized quinolines through Vilsmeier cyclization (Scheme 11, lower equation). Both cyclizations were facile with *N,S*-acetals bearing strongly activating groups on aniline. The resulting 2-methylthio-quinolines could be further manipulated, by dethiomethylation with Raney nickel, or replaced by various

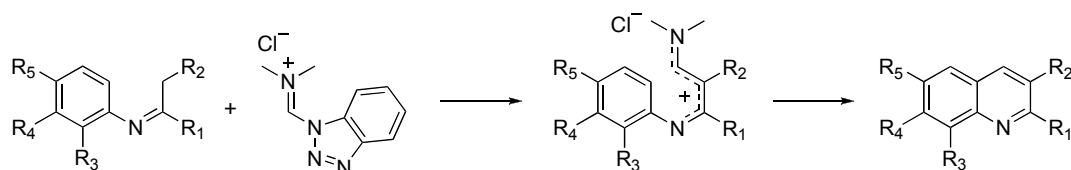
nucleophiles to generate 2-alkyl, aryl or amino quinolines.^{38,39} Wang also reported using remarkably similar α -aroylketene dithioacetals with *o*-aminobenzoic acids to generate 2-methylthio-3-arylquinolones.⁴⁰

Scheme 11



Katritzky demonstrated an improved Vilsmeier-type cyclization using benzotriazole iminium salts and *N*-arylimines. The resulting vinamidium salts were readily transformed into 2- and 3-alkyl quinolines through a tandem cyclization-elimination process in refluxing THF (Scheme 12).⁴¹

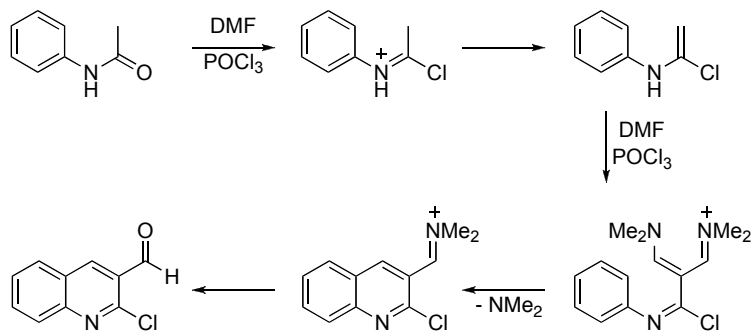
Scheme 12



In 1995, Otto Meth-Cohn reviewed his longstanding “Vilsmeier Approach” and described a newer “Reverse Vilsmeier Approach” to quinolines. The “Vilsmeier Approach” converted acylanilides to α -chloroenamines with POCl₃, then used *N,N*-

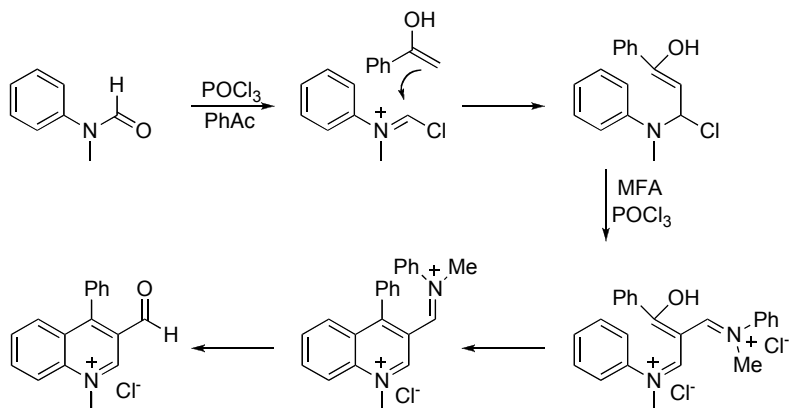
dimethylformamide to formylate the enamines. After electrocyclization, the quinoline ring was formed, producing 2-chloro-3-formyl-quinolines (Scheme 13).

Scheme 13



In Meth-Cohn's "Reverse Vilsmeier Approach," *N*-methylformanilide was used to form a Vilsmeier reagent, and reacted with electron-rich alkenes. After reaction with a second equivalent of Vilsmeier reagent, cyclization occurred to form *N*-methylquinolinium salts.⁴²

Scheme 14



Focusing solely on the reaction conditions, improvements to the Skraup/Doebner-von Miller processes have been recently achieved using solid-phase, two-phase, and vapour-phase procedures. In 2003, Ranu et al., reported a microwave-assisted, solvent-free Doebner-von Miller synthesis of 4-alkylquinolines. His conditions utilized the aniline and alkyl vinyl ketone adsorbed onto silica gel impregnated with indium chloride. After short microwave irradiation, excellent yields of 4-alkylquinolines were obtained, using a variety of alkyl, alkoxyl, hydroxyl and halide substituted anilines. This technique was also demonstrated to be effective at making alkyldihydroquinolines, using β -disubstituted alkyl vinyl ketones.^{43,44} Kidwai also reported a solid-phase, microwave-assisted synthesis of 2,4-alkylquinolines. A preformed vinylous amide condensed from chlorofluoroaniline and α,β -unsaturated methyl ketone was cyclized on acidic alumina, under solvent-free conditions. This led to clean quinoline product without the use of mineral acids or toxic organic solvents.⁴⁵

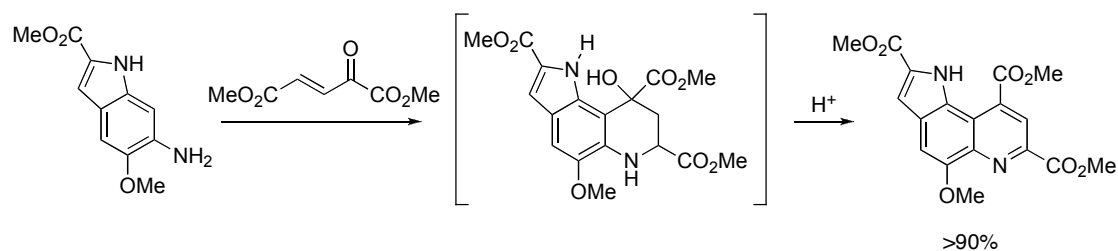
Matsugi and coworkers developed a two-phase protocol for the Doebner-von Miller synthesis. Their production of 2-alkyl quinolines was optimized using a toluene/6M HCl two-phase reaction medium. The α,β -unsaturated aldehyde remained in the toluene phase, until protonated at the phase interface. The protonated anilines remained in the aqueous phase. This setup prevented the polymerization of the aldehydes which usually plagues the Doebner-von Miller reaction, both in yield, and in product isolation.⁴⁶ Li also reported a two-phase Doebner-von Miller reaction using similar conditions. Li used 12N HCl, toluene, and a phase-transfer catalyst. In their work, 5 mol % of triethylbenzylammonium chloride produced optimal yields of

the desired 2-methyl-8-quinoline carboxylic acid.⁴⁷ Similar yield and product isolation improvements were noted.

Vapour phase protocols for quinoline synthesis have also been reported as an improvement to the Skraup synthesis of alkylquinolines. In 1997, Campanati developed a procedure using acid-treated K10 Montmorillonite clay, gaseous ethylene glycol and 2-ethylaniline. This heterogeneous catalysis produced 2-methyl-8-ethylquinoline regioselectively, and also verified the crotonaldehyde intermediate proposed by Doebner-von Miller. Yields were modest, but were reported based on the amount of ethylene glycol used, as opposed to that of the aniline starting material.⁴⁸

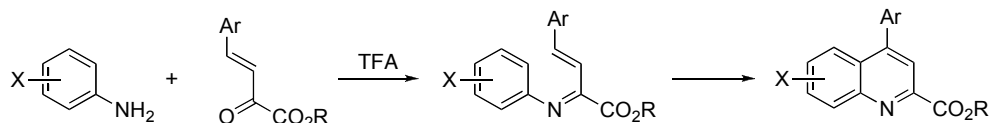
Applications of modified Doebner-von Miller syntheses have also been reported. Carrigan reported the application of a process initially reported by Corey (Scheme 15),⁴⁹ using dimethyl oxoglutaconate as the three-carbon unit. This procedure produced twenty-six quinoline-2,4-dicarboxylic acids that were subsequently screened for activity as inhibitors of glutamate vesicular transport protein.⁵⁰ Zhang also used the Corey modification, using dimethyl oxoglutaconate and a 3-methoxyaniline. Instead of the quinoline formation, Zhang observed addition at the position *para* to the amino group. This product could not cyclize in a Doebner-von Miller manner, and was reported as a possible alternative mechanism for the reaction, proposing that the benzenoid addition may occur first followed by cyclization. However this proposal was specifically caveated by the uniqueness of the substrate used, both due to electronics of the electron-rich arene and the sterics of their 5,6-indole ring.⁵¹

Scheme 15



Wu recently reported an application of the Skraup/Doebner von Miller reaction demonstrating a reversal of the typical regioselectivity. Condensing γ -aryl- β,γ -unsaturated α -ketoesters with anilines produced 4-aryl-2-carboxylquinolines (Scheme 16), not the expected 2-aryl-4-carboxyquinolines. Wu proposed a direct 1,2-addition of the aniline to form an anil which Eisch observed to not cyclize (see top of Scheme 2). However, Wu hypothesized that the additional electron-withdrawing nature of the ester group facilitated a direct electrophilic ring closure, forming the observed 4-aryl-2-carboxyquinoline after oxidation.⁵²

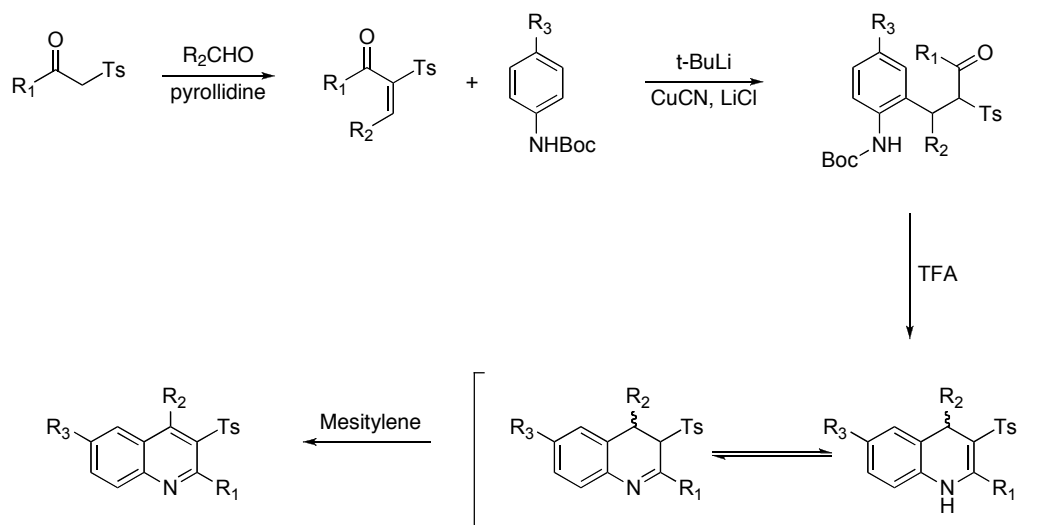
Scheme 16



The use of α -tolylsulfonyl- α,β -unsaturated ketones was demonstrated by Swenson to produce 2,4-aryl and alkyl quinolines (Scheme 17). In this case, the combination of directed-*ortho*-metalation, and the placement of the tolylsulfonyl leaving group

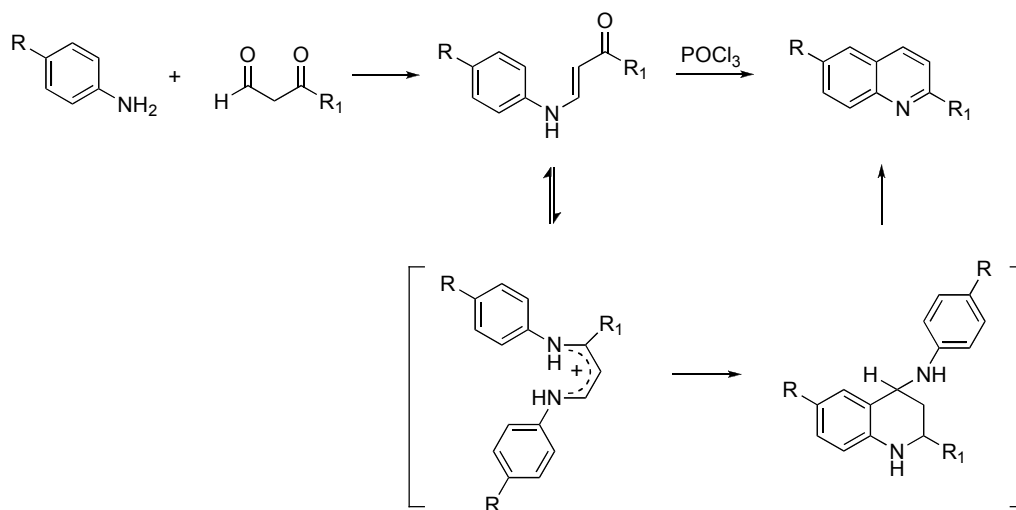
produced excellent regioselectivity at the 2- and 4- positions of the product quinolines.⁵³

Scheme 17



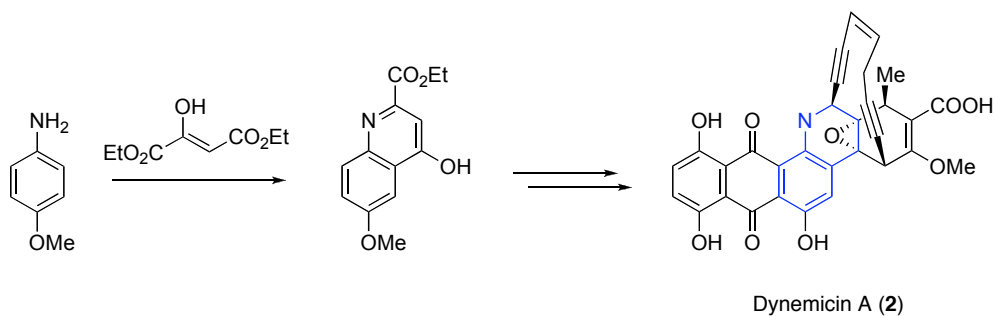
Perfluoroalkylquinolines have been produced, and the mechanism of such a cyclization has been studied and reported by Schlosser, et al.⁵⁴ Perfluoroalkyl-1,3-dicarbonyls were linked to anilines, and a mechanistic study was conducted to explain the production of high yields of the unexpected 2-substituted quinolines (Scheme 18). Amine randomization was the explanation for the perceived “walking” of the perfluoroalkyl group from the 4- to 2-position during cyclization (Scheme 18).

Scheme 18



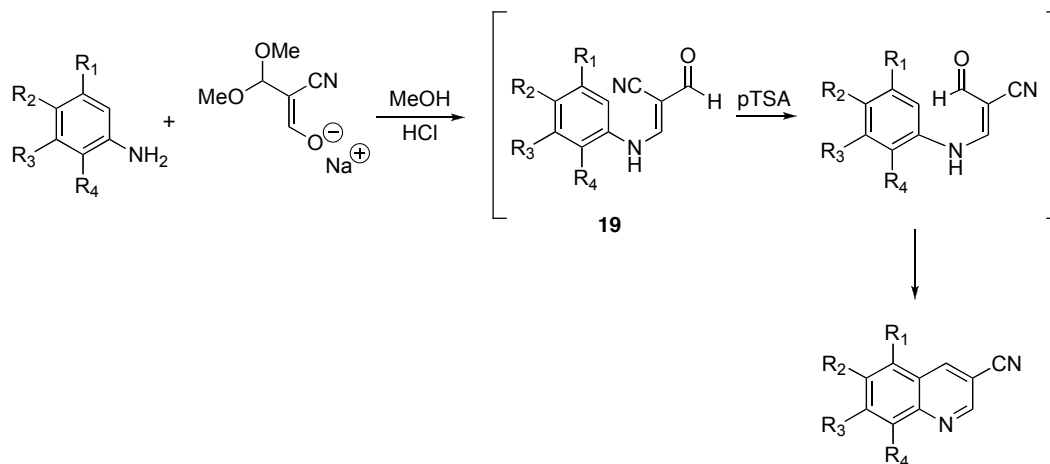
Recent applications of modified Conrad-Limpach-Knorr and Combes reactions are more rare than that of Skraup and Doebner-von Miller. In 2003, Schlosser's group, along with the aforementioned mechanistic study, reported on the preparation of a range of trifluoromethyl-substituted quinolines, using ethyl trifluoroacetoacetate. After subsequent transformations, this Conrad-Limpach-Knorr type, acid-catalyzed condensation with anilines produced high yields of the desired trifluoromethyl quinoline carboxylic acids.⁵⁵ In 1996, Nicolaou and coworkers used the Conrad-Limpach-Knorr reaction in their partial synthesis of the CDE ring of dynemicin A (**2**). In this example, *p*-anisidine was reacted with diethyl oxalacetate under acidic conditions, and thermally cyclized to the desired 2-carboethoxy-4-hydroxyquinoline in 75% yield (Scheme 19).⁷

Scheme 19



In 1998, Charpentier developed a synthesis of 3-cyanoquinolines using 3,3-dimethoxy-2-formyl-propanenitrile sodium salt as a 1,3-diformyl-2-cyano synthon. This modified Combes procedure initially produced the *Z*-isomer **19** (Scheme 20), which would not cyclize. After optimization, treatment with *p*-toluene sulfonic acid catalyzed both isomerization and cyclization in good yield (60-68%).⁵⁶

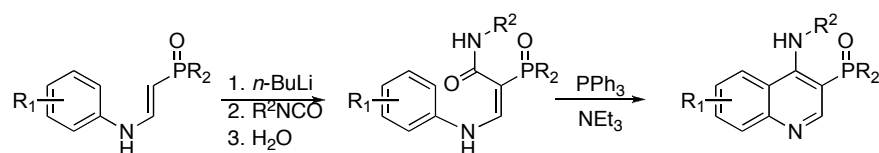
Scheme 20



Lastly, 4-aminoquinolines can be produced from anilines using a procedure developed by Palacios.^{57,58} These 4-aminoquinolines form the base set of antimalarial

agents, like chloroquine (**9**), and are highly desirable synthetic targets. The key to Palacios' procedure is the addition of lithiated β -enamino phosphonates to isocyanates to form the functionalized amides, which when treated with triphenylphosphine and hexachloroethane in the presence of triethylamine cyclize to the desired 4-aminoquinolines. The resulting 3-phosphonyl group was also proposed to be a key to the observed biological activity of these 4-aminoquinolines.

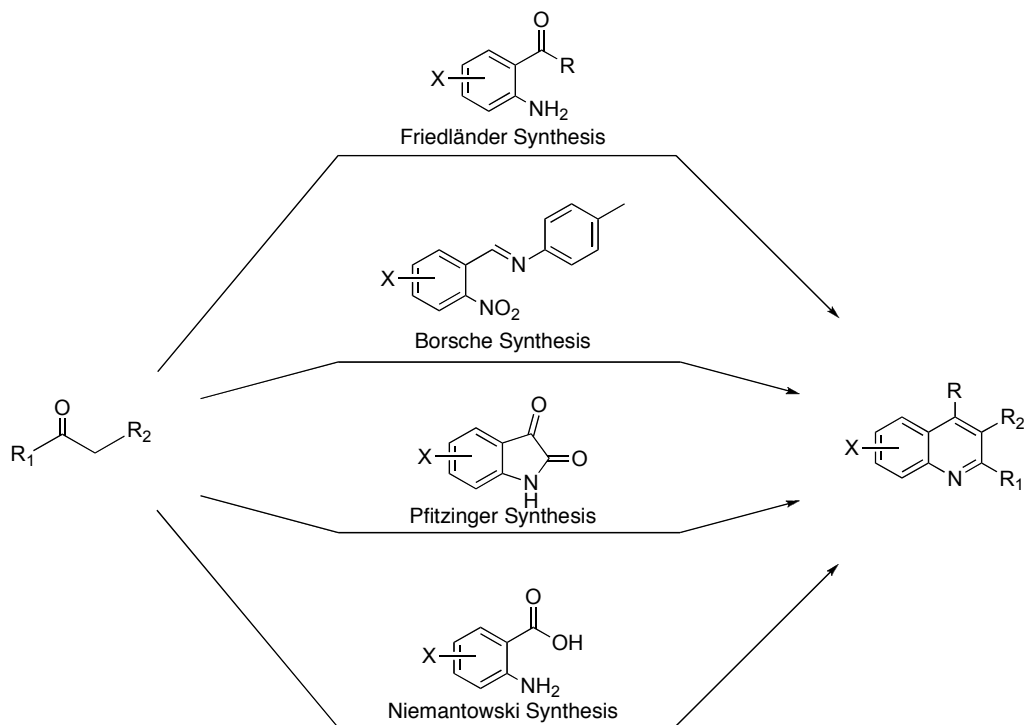
Scheme 21



FRIEDLÄNDER AND FRIEDLÄNDER-LIKE TECHNIQUES

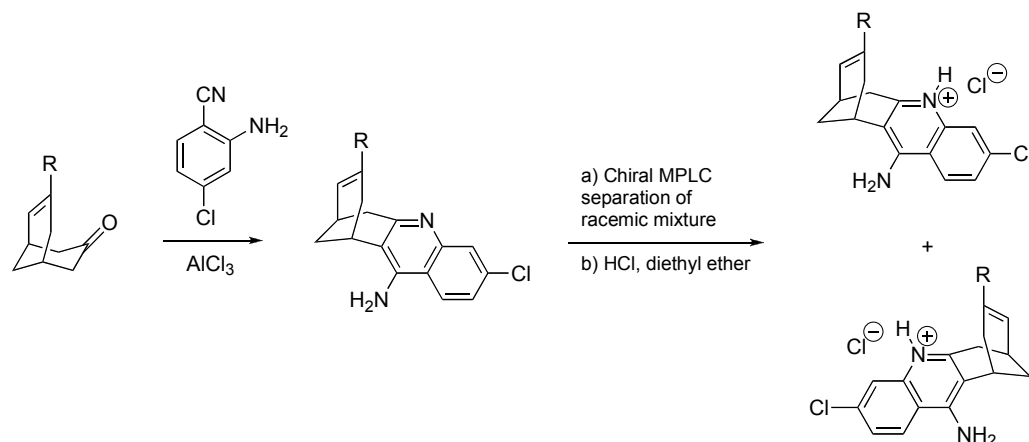
The second major class of quinoline syntheses start with *ortho*-substituted anilines, and are based on variations of the Friedländer synthesis, including the Pfitzinger, Niemantowski and Borsche syntheses. Since its initial discovery in 1882, the Friedländer synthesis is by far the most widely applied, and modified, quinoline synthesis to date.⁵⁹ The basic Friedländer reaction involves the condensation of *o*-aminobenzaldehyde or *o*-amino benzyl ketone with the two carbons derived from an α -methylene carbonyl unit. The major variants of the Friedländer vary not in the methylene carbonyl, but in the starting aniline derivative. The Borsche reaction⁶⁰ starts with arylimines, the Pfitzinger reaction⁶¹ starts with isatin, and the Niemantowski reactions²⁴ starts with *o*-aminobenzyl carboxylic acids (Scheme 22).

Scheme 22



Examples of the use of the Friedländer reaction can be found throughout the literature. One of the earlier, notable examples was reported by Bracke. In 1969, a polycondensation of 4,6-diaminoisophthalaldehyde with *p*-diacetylbenzene, 2,6-diacetylpyridine, and bis(*p*-acetyl-phenyl) ether resulted in thermally stable anthrazoline polymers.⁶² In the same time frame, Parfitt reported the synthesis of benzo[a]phenanthrolines prepared by a double Friedländer condensation of 2,2'-diaminobenzophenone with β -diketones.⁶³ In two major natural product syntheses published in the early 1980s, Weinreb and Kende both used Friedländer reactions to assemble the AB quinoline ring in their synthesis of streptonigrin (**1**).^{4,5,64} These two works will be thoroughly reviewed in a later section. More recently, the synthesis of an inhibitor of HMG-CoA (the rate-limiting enzyme in sterol biosynthesis in animals and plants) was conducted by Suzuki, using a Friedländer synthesis of the 2-cyclopropyl-4-(*p*-fluorophenyl)-3-quinoline carboxylic ester intermediate.⁶⁵ This *p*-toluenesulfonic acid catalyzed condensation produced the desired product in 90% yield, and was suitable for the proposed industrial scale up of this synthesis. In 2000, Camps targeted the synthesis of an acetylcholinesterase inhibitor, dubbed huprine X, as a potential treatment for Alzheimer's disease. This synthesis relied on a Friedländer condensation of 4-chloro-2-aminobenzonitrile with their previously developed bicyclononenone, to afford the desired bicycloquinoline in 41% isolated yield (Scheme 23).⁶⁶

Scheme 23

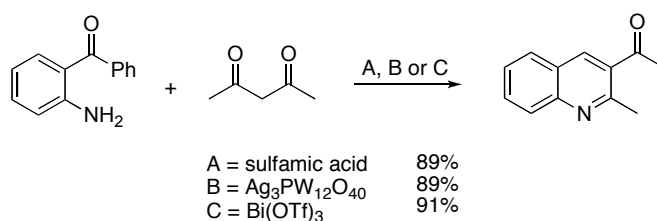


As was seen in the Skraup/Doebner-von Miller syntheses, the Friedländer approach has been limited only by the availability of the starting materials, and the harshness of the reaction conditions. Many recent works have focused on improving those reaction conditions, including various solvent and solvent-free systems, newer catalyst applications, and more robust and versatile starting materials than the relatively unstable *o*-aminobenzaldehydes.

Work emerging from the Yadav group at the Indian Institute of Chemical Technology has highlighted several examples of such conditions improvements. In 1997, solvent-free, clay-catalyzed Friedländer reactions were been developed. These heterogeneous reactions produced yields equivalent to those reported in the literature for similar transformations in solvent, with significantly shorter reaction times, and cleaner product isolations.⁶⁷ In 2005, Yadav outlined the use of sulfamic acid as a heterogeneous catalyst in Friedländer condensations. In this solvent-free procedure, both cyclic and acyclic alkyl ketones were condensed with *o*-aminobenzophenones to produce a variety of 2,3-alkyl-4-phenylquinolines in excellent yield, with only

filtration of the solid catalyst and recrystallization of the product necessary for purification (Scheme 24).⁶⁸ Yadav's group also developed the use of silver phosphotungstate as a heteropolyacid catalyst for the Friedländer condensation of 2-aminobenzophenone with acetyl acetone. This reaction produced an exceptional 89% yield, in 4.5 hours.⁶⁹ Yadav's group also reported the use of 5 mol % bismuth(III) triflate as a catalyst for the same Friedländer reaction, reporting virtually the same improvements: 91% yield in 4h, in room temperature ethanol. This is a dramatic improvement over traditional acid-catalyzed reactions that require refluxing conditions, and significantly longer reaction times.⁷⁰

Scheme 24

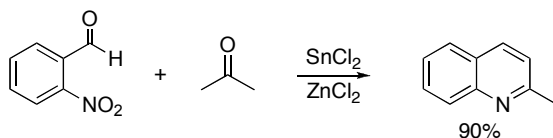


As a purported improvement over this $\text{Bi}(\text{OTf})_3$ catalysis, De and Gibbs applied $\text{Y}(\text{OTf})_3$ as a catalyst in a similar condensation of *o*-aminobenzophenone with ethyl acetoacetate, reporting 89% yield in 4h in room temperature acetonitrile.⁷¹ In 2003, Arcadi reported the use of gold(III) catalysts in a “green” approach to the Friedländer synthesis. By using 2.5 mol % of $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ in ethanol at 40 °C, the condensation of *o*-aminobenzophenone with ethylacetoacetate was completed in 6h with an 83% yield.⁷² Most recently, in 2007, Zhang and Wu outlined a “Lewis acid-surfactant-combined catalyst” Friedländer annulation using aqueous scandium

tris(dodecyl sulfate),⁷³ and Dabiri reported a solvent-free Friedländer synthesis catalyzed by oxalic acid.⁷⁴

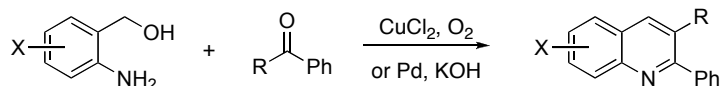
Along with improved catalysts, the Friedländer synthesis has been extensively modified by numerous investigators to improve the yield, and limit the byproducts of this sequence. Kadin reported a relatively early example of such a modification in 1984, where *o*-nitrobenzaldehydes were used as starting material, based on their easier preparation and storability over *o*-aminobenzaldehydes. Kadin used a modified Wittig reaction to convert *o*-nitrobenzaldehydes to *o*-nitrobenzyl alkenes, which cyclize to produce quinoline-2,3-dicarboxylate *N*-oxides. After reduction of the *N*-oxide, the desired quinoline-2,3-dicarboxylates are isolated in moderate yields.⁷⁵ Another novel route to quinoline synthesis involved starting with nitro aryl aldehydes, and reducing the nitro group to aniline *in situ*, in the presence of the enolizable carbonyl compound. McNaughton proved that strategy successful by using a combination of 5 eq each of SnCl₂ and ZnCl₂. This combination reduced the nitro group of *o*-nitrobenzaldehyde, and in the presence of various symmetrical ketones, produced the desired 2,3-alkylquinolines in high yield (82-94%) (Scheme 25).⁷⁶ This approach was mirrored by Li in 2007 using Fe/HCl as the reducing agent, producing a broad set of 2-alkyl, -alkenyl, -aryl and -heteroaryl quinolines.⁷⁷

Scheme 25



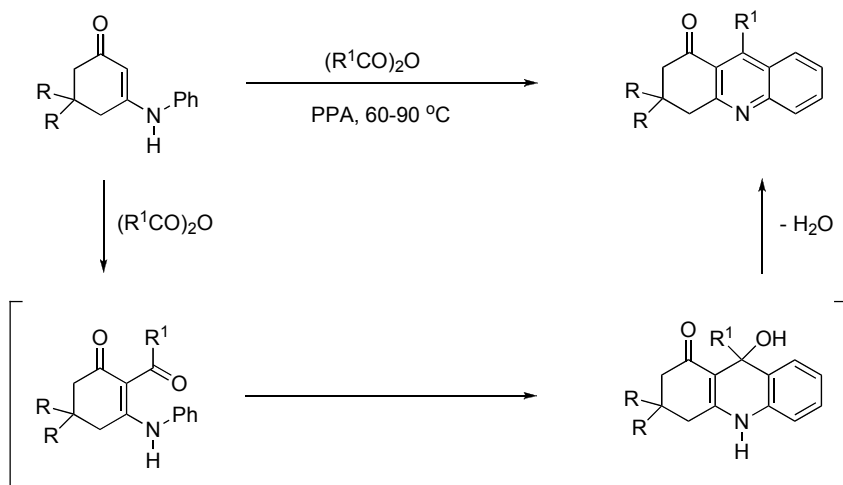
In two recent reports by Cho, *o*-aminobenzaldehydes were also produced *in situ*, by the catalytic oxidation of *o*-aminobenzyl alcohols (Scheme 26). In the presence of a variety of ketones, 2- and 2,3-substituted quinolines were produced by this modified Friedländer technique in good yield.^{78,79}

Scheme 26



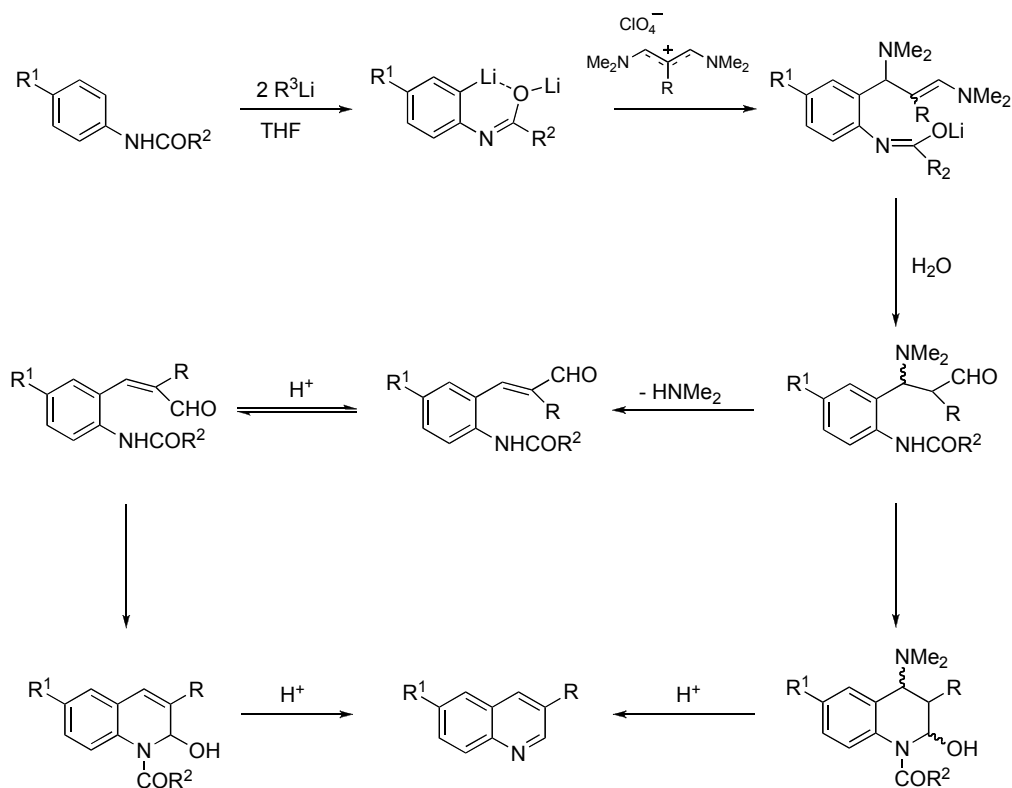
With the goal of improving the breadth of products available, Na *et al.* introduced a Friedländer variation that used *N*-phenyl enaminones and alkyl anhydrides as the starting materials. This reaction allowed the creation of 4-alkyl-2,3-carbocyclic quinolines, where the new 2,3-carbocycle was derived from the original enaminone, and could be robustly built up prior to the Friedländer condensation (Scheme 27).⁸⁰

Scheme 27



Muchowski and coworkers achieved a widely referenced modification to the Friedländer reaction, by condensing *ortho*-lithiated Boc- and Piv- protected anilines with 4 different masked malondialdehydes derivatives to produce 3-aryl and alkyl substituted quinolines in good to excellent yield (Scheme 28). This approach benefited from the ease of producing *N*-acylarylamines, the ready availability of the masked malondialdehyde precursors, and the facile nature of the cyclization.⁸¹

Scheme 28

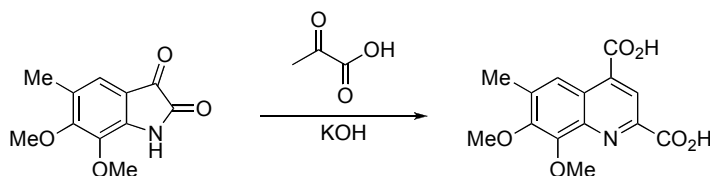


Two recent papers by Ubeda and Chelucci applied this *ortho*-lithiated aniline strategy in a similar manner, however they both first used DMF to formylate the aniline, followed by subsequent condensation with enolizable carbonyl compounds to

form quinolines. Ubeda used a variety of aryl and alkyl ketones and aldehydes in the second step, but had better success with the ketones, forming 2,3-alkyl and aryl quinolines in good yield. Forming 3-unsubstituted quinolines using enolized aldehydes were less successful, due to noted secondary reactions. Ubeda's procedure also benefited from facile *N*-deprotection of the pivaloyl group.⁸² In the work of Chelucci, Boc-protected anilines were similarly *ortho*-lithiated with *t*-BuLi and formylated with DMF, to produce the Friedländer-esque *o*-aminobenzaldehydes. Those intermediates were not isolated, but immediately treated with the enolates of various ketones, and refluxed in 3N HCl to produce the desired alkyl and aryl quinolines in varied yields (29-85%).⁸³

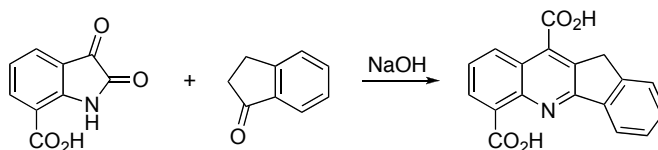
The Pfitzinger reaction is also a widely used variation of the Friedländer reaction, using isatin derivatives instead of *o*-aminobenzaldehydes. As early as 1954, Henze investigated the regioselectivity of the Pfitzinger reaction using unsymmetrical alkyl ketones.⁶¹ In 1982, Weinreb applied the Pfitzinger reaction to the synthesis of methoxatin (**16**) (Figure 4), a coenzyme in several bacterial alcohol dehydrogenases. The Pfitzinger reaction of 6,7-dimethoxy-5-methyl isatin with pyruvic acid under basic conditions (using KOH), afforded the desired diacid (Scheme 29), which was immediately converted to the diester, with an overall 50% yield for the two steps. Subsequent transformations, including an "umpolung" variation of the Reissert indole synthesis for annulation of the remaining pyrrole ring, afforded methoxatin (**13**) in 13 steps.⁸⁴

Scheme 29



Other examples of the application of the Pfitzinger reaction include two publications by Deady and coworkers, in the synthesis of new topoisomerase I and II inhibitors. The work focused on making new non-linear tetracyclic quinolines with inhibitory activity similar to doxorubicin and DACA. The synthesis of these putative inhibitors was conducted using Pfitzinger reactions of isatin-7-carboxylic acid with various substituted 1-indanones, in a 10% NaOH solution for 1h (Scheme 30). Although the bulk of the data focused on structure-activity evaluations, the unoptimized yields were still good (54-74%).^{85,86}

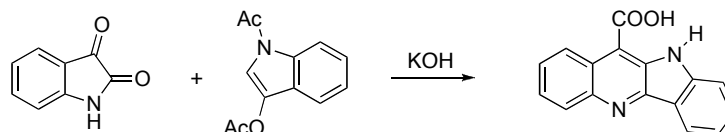
Scheme 30



In 2001, Wright and coworkers reported the use of the Pfitzinger reaction to synthesize 15 derivatives of the indoloquinoline alkaloid cryptolepine (**17**) (Figure 4). These derivatives were hoped to lack the DNA intercalating cytotoxicity of cryptolepine, while retaining the chloroquine-like antiparasitoid properties that make cryptolepine an effective treatment of malaria. Isatin was condensed with *O,N*-

acetylindoxyl in the presence of KOH under oxygen-free conditions to produce quindoline-11-carboxylic acid (Scheme 31).⁸⁷

Scheme 31

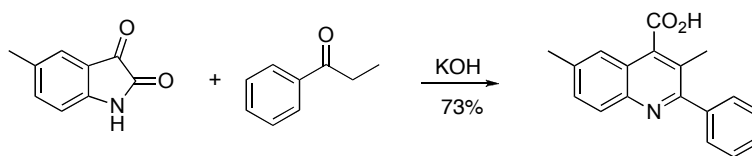


Ivachtchenko's work in 2004 demonstrated both a utilization and mechanistic study of a unique product observation in the Pfitzinger reaction. Using 5-sulfamoylisatins and diethyl malonate, their Pfitzinger reaction produced 6-sulfamoyl-4-quinoline carboxylic acids, instead of the anticipated 2-oxo-1,2-dihydroquinoline-4-carboxylic acid. Their mechanistic studies including isotopic labeling and dynamic LCMS measurements proved that the ethanol co-solvent was incorporated into the new quinoline ring system instead of the methylene from the diethyl malonate. Using ¹³C labeling of both the ethanol and diethyl malonate, in separate experiments, they were able to clearly identify the ethanol carbon in the quinoline ring.⁸⁸

Finally, Boa reported the use of the Pfitzinger reaction to generate a series of 2-phenyl-quinoline-4-carboxylic acid derivatives, related to the human dihydroorotate dehydrogenase (DHODH) inhibitor brequinar (**18**) (Figure 4). The malarial parasite *P. falciparum* does not have the ability to salvage pyrimidines and relies on the *de novo* synthesis of uridine monophosphate to grow. One of the enzymes required in that biosynthesis is DHODH, and therefore potential inhibitors of this enzyme have

become favorable targets in the search for new antimalarial chemotherapies. Brequinar is a known inhibitor of the human DHODH, and was used a baseline for designing *P. falciparum* DHODH inhibitors. The series of brequinar analogues were producing by base-catalyzed Pfitzinger reaction of 5- and 7-methylisatins with methyl and ethyl phenyl ketones, in the presence of KOH in ethanol and water, generating the desired 2-phenylquinoline-4-carboxylic acids, with methyl groups varied at the 3-, 6- and 8- positions, in excellent (73-90%) yields.⁸⁹

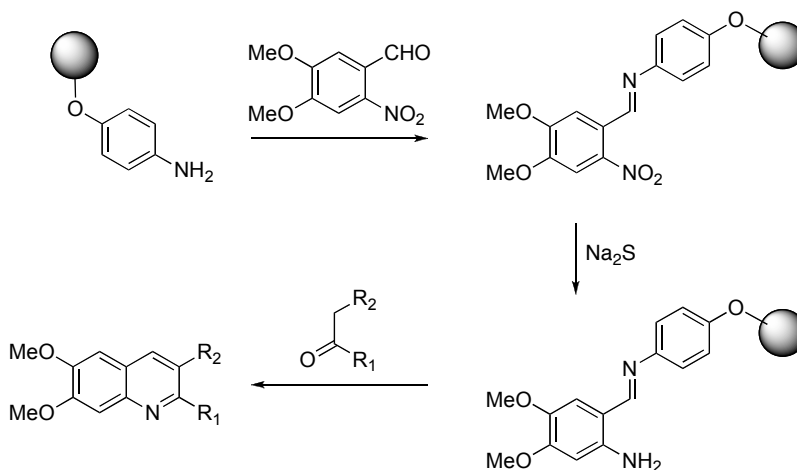
Scheme 32



The Niemantowski and Borsche variations, substituting *o*-aminobenzyl carboxylic acids and *o*-aminoarylimines for *o*-aminobenzaldehydes, respectively, have been applied or reexamined considerably less often than the Friedländer and Pfitzinger reactions. One very recent example of the Borsche modification was used to attach quinoline precursors to TentaGel-Br resin, and generate the desired dimethoxyquinolines in a parallel solid-phase support sequence. In this example, the desired resin-supported Borsche azomethine was generated by treatment of the free resin with 3,4-dimethoxy-6-nitrobenzaldehyde in refluxing ethanol. After reduction of the nitro group with sodium sulfide, typical Borsche conditions—refluxing ethanol in the presence of piperidine—was used to condense a variety of ketones with the resin-bound “masked” *o*-aminobenzaldehyde, to form the desired 3-acyl-2-

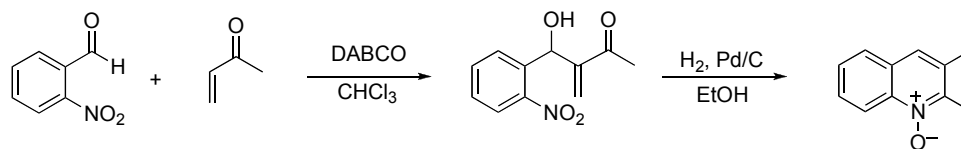
alkylquinolines in excellent yield (Scheme 33). The expected facile purification, by simple filtration, made this technique attractive for the synthesis of such quinolines.⁹⁰

Scheme 33



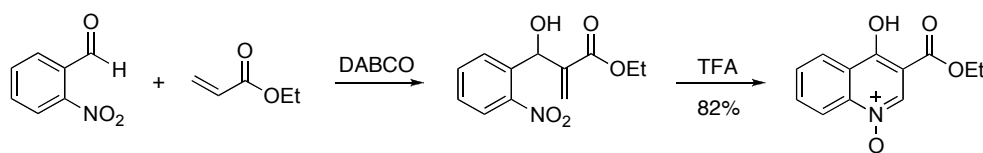
Another Friedländer-like method that has been used in several recent studies is the Baylis-Hillman methodology. Using α,β -unsaturated ketones, condensing them with *o*-nitrobenzaldehydes in a Baylis-Hillman fashion, results in the addition of a two-carbon unit, which is still susceptible to attack by nitrogen nucleophiles to complete the quinoline system. In Familioni's work (Scheme 34), *o*-nitrobenzaldehyde was treated with methyl vinyl ketone, methyl acrylate and ethyl acrylate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to afford the desired Baylis-Hillman adducts. After reduction of the nitro group with H_2 and 10% Pd/C, the anticipated cyclization occurred in good yield to produce the expected quinoline-*N*-oxides.⁹¹

Scheme 34



This Baylis-Hillman approach was also used in two publications out of the Jae Nyoung Kim group from Chonnam National University. In the first publication, reaction of their Baylis-Hillman acetates with tosylamide in the presence of potassium carbonate afforded the desired quinolines in 55% yield. This one-pot reaction occurs through sequential reaction of the Baylis-Hillman acetate with the tosylamide, followed by nucleophilic aromatic substitution with the *ortho*-substituted halogen to form a tosylamidodihydroquinoline, followed by elimination of the *p*-toluenesulfonic acid to form the desired quinoline. The final elimination is not as facile as desired, and some dihydroquinoline (2-10%) was isolated.⁹² In Kim's second publication, their Baylis-Hillman acetate is directly cyclized with the *o*-nitro group using catalytic triflic acid (Scheme 35). Two mechanisms are proposed to account for the observed production of 3-acyl-4-hydroxyquinoline-*N*-oxides, with the authors favoring the *N*-hydroxyisoxazoline intermediate.^{93,94}

Scheme 35

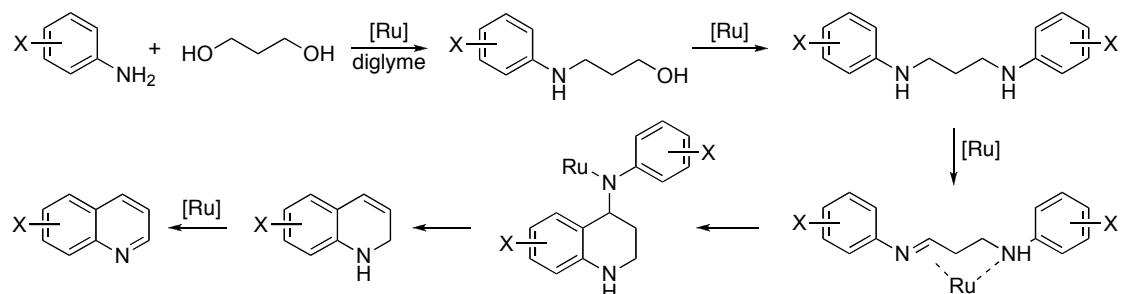


ORGANOMETALLIC TECHNIQUES

Besides the aforementioned Skraup and Friedländer methods, the use of organometallic reagents has played a dominant role in quinoline syntheses, in a manner similar to the rest of synthetic organic chemistry. These organometallic reactions include amine exchange reactions, nitro group reductions catalyzed by a variety of metals, metathesis reactions, and coupling reactions.

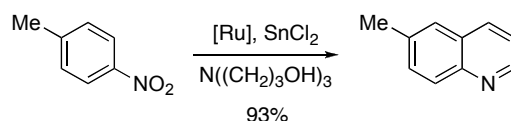
The earliest noted example was by Tsuji in 1987. This work demonstrated that substituted anilines react with 1,3-propanediol, in refluxing diglyme, in the presence of a catalytic amount of ruthenium trichloride hydrate ($\text{RuCl}_3 \cdot n\text{H}_2\text{O}$)-tributylphosphine (PBu_3) to give quinolines in modest yields (37-59%). The proposed mechanism of such a transformation included *N*-alkylation of both hydroxyl groups of the diol, forming a propylenediamine intermediate, which underwent ruthenium-catalyzed dehydrogenation to the imine, and after electrophilic substitution from the second amine, formed the dihydroquinoline. This dihydroquinoline was dehydrogenated again by ruthenium to form the product quinoline (Scheme 36).⁹⁵

Scheme 36



A number of ruthenium-catalyzed quinoline syntheses has been reported by the group led by Chan Sik Cho at Kyungpook National University. Their first two reports utilized anilines and triallylamines and trialkylamines in a cascade amine exchange reaction, similar to Tsuji's observations. The amine transferred, dehydrogenated to form ruthenium-iminium complexes, and finally cyclized to form 2,3-alkyl-quinolines in good yield.^{96,97} In their more recent examples, a consecutive reduction of nitroarenes and cyclization with amino alcohols, catalyzed by ruthenium, formed a variety of substituted quinolines in excellent yield (Scheme 37). Unlike the Tsuji work, their process required a catalytic amount of SnCl₂, for unknown reasons. The SnCl₂ appeared to be necessary for both the reduction and cyclization steps.^{98,99}

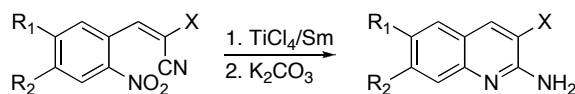
Scheme 37



The reduction of a nitro group, followed by cyclization, is a methodology used by several other groups besides Cho. In Zhang's group, both titanium(IV) chloride and samarium(II) iodide have been used in such a manner. In the case of titanium, a combination of TiCl₄/Sm was used to selectively reduce aromatic nitro groups to anilines in the presence of a vinyl cyano group, which induced cyclization with the cyano group to form 2-aminoquinolines in excellent yield (Scheme 38).¹⁰⁰ In two subsequent reports, SmI₂ was used to reduce aryl nitro groups to anilines, and subsequently induce cyclization to form quinolines. In the first such example, SmI₂ was used in manner analogous to the titanium work, selectively reducing the nitro group in the presence of the cyano group, and inducing cyclization to form 2-

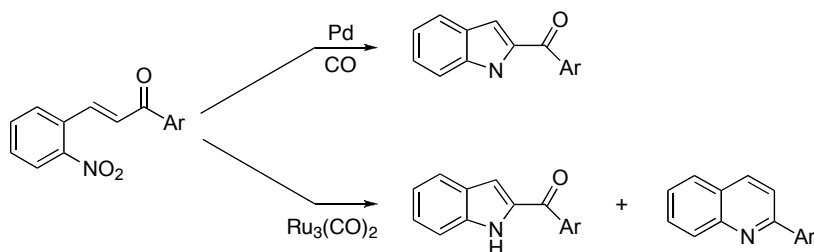
aminoquinolines.¹⁰¹ In the second example, 2-nitro-1,3-diphenyl-2-propen-1-ones were reduced, forming 2-methylquinoline.¹⁰²

Scheme 38



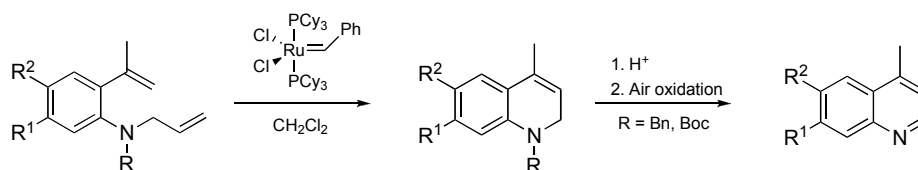
Other authors have reported nitro group reductions, followed by condensation with an *ortho*-functionalized aldehyde chain to produce quinolines. In the work by Boix, 2-nitrocinnamaldehyde was reduced by Zn/H₂O in a high temperature/pressure reactor, and cyclization afforded quinoline in high yield. Subsequent reduction of quinoline was minimal, and only a small fraction of tetrahydroquinoline was isolated. In contrast, the analogous ketones and carboxylic acids formed significantly more over-reduced tetrahydroquinolines, limiting the use of this technique.¹⁰³ In the work by Banik, the nitro group reduction was mediated by indium in the presence of ammonium chloride, producing quinolines in excellent yield (~90%).¹⁰⁴ In 1996, Cenini used ruthenium-catalyzed carbonylation of 2-nitrochalcones to attempt to form indoles, however a significant by-product of such conditions was the reduction of the nitro group to an aniline, which could similarly condense with the α,β -unsaturated ketone to produce 2-arylquinolines in good yield (46-85%) (Scheme 39).¹⁰⁵ In work by Banwell in 2004, palladium-catalyzed Ullman cross-coupling of β -halo-enals with bromonitrobenzenes formed *o*-nitrocinnamaldehyde, which could be reductively cyclized by H₂ with Pd/C to form quinolines.¹⁰⁶

Scheme 39



Ring-closing metathesis (RCM) has also been used as an organometallic route to quinolines. In 2001 and 2004, Arisawa reported the synthesis of quinolines starting from *N*-allyl-*N*-protected-*o*-aminostyrenes, using second and fourth generation Grubbs' catalysts to induce the RCM (Scheme 40). In each case, the yields were outstanding, and the *N*-protecting groups were removed by air oxidation following purification.^{107,108} In 2005, the same group applied this RCM technique to the total synthesis of the tetrahydroquinoline (+)-(*S*)-angustureine. This unnatural enantiomer was used to determine the absolute stereochemistry of this antimalarial and anti-mycobacterial natural product.¹⁰⁹

Scheme 40



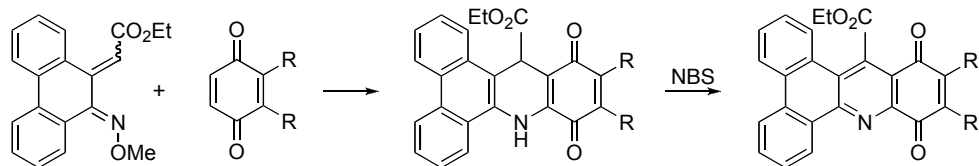
Other more isolated examples of organometallic reactions in quinoline formation have been noted. In Amii's work, Rh(I) complexes were found to catalyze the coupling cyclization of *N*-aryl trifluoroacetimidoyl chlorides with alkynes to afford 2-

trifluoromethylated quinolines in good yields.¹¹⁰ In 2002, Jiang reported a zinc(II)-mediated alkynylation-cyclization of *o*-trifluoroacetyl anilines to form 4-trifluoromethyl-quinolines.¹¹¹ Diallylanilines have been converted to dialkylquinolines by $\text{Co}_2(\text{CO})_8$ by Jacob and Jones.^{112,113} Also, β,β -difluoro-*o*-isocyanostyrenes have been demonstrated to react with organomagnesiums or organolithiums to generate an sp^2 carbanion on the isocyano carbon, which can cyclize via substitution of one of the fluorides, leading to 3-fluoroquinolines. This cyclization is possible due to the unique reactivity of *gem*-difluoroalkenes toward nucleophilic substitution via an addition-elimination process.¹¹⁴ A similar, but reverse-polarity transformation was done with lithiated *o*-isocyano- β -methoxystyrenes where the isocyano group was attacked by the carbon nucleophile to form 3-methoxyquinolines.^{115,116}

CYCLOADDITIONS

Electrocyclic reactions have also played a significant role in the synthesis of quinolines. The most noteworthy examples used the Diels-Alder reaction. In the 1994 work by Nicolaides, two isomeric ethyl [10-(methoxyimino)phenanthren-9-ylidene]acetates were reacted with two dienophiles, 1,4-benzoquinone and 1,4-naphthoquinone to form tetrahydroacridine carboxylates in excellent yield (Scheme 41). The same diene was also reacted with maleic anhydride to form a analogous Diels-Alder adduct.¹¹⁷

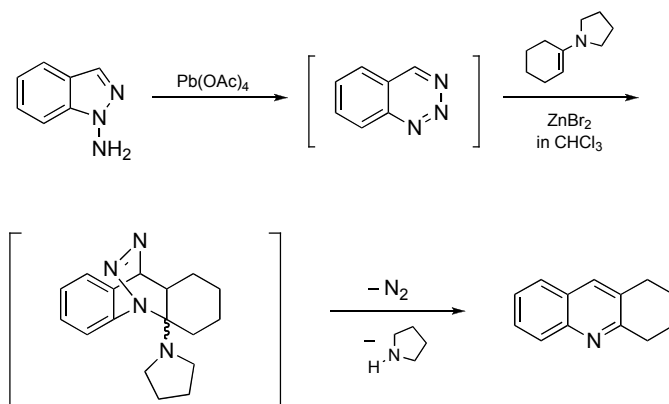
Scheme 41



In 2002, Yadav reported the InCl_3 -catalyzed aza-Diels-Alder reaction of 3,4-dihydro-2H-pyran (DHP) with aryl amines to form tetrahydropyranoquinolines in excellent yield (70-90%). The *in situ* generated aryl imines react selectively to form predominately endo products, and the reaction is generally mild and fast (~4h).¹¹⁸

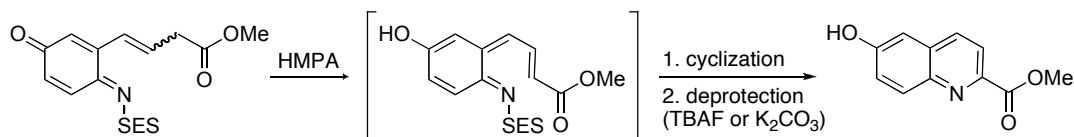
Purportedly the first example of asymmetric tetrahydroquinoline synthesis by the inverse electron demand Diels-Alder reaction was reported by Sundararajan *et al.* in 2001. In this work, benzylidene aniline was reacted with various dienophiles in the presence of a chiral titanium catalyst to produce moderate yields, but poor to modest diastereo- and enantioselectivities. Dihydropyrans, dihydrofurans, cyclopentadienes and ethyl vinyl ethers were used as dienophiles, with similar results.¹¹⁹ The work of Koyama and coworkers applied the Diels-Alder reaction to 1,2,3-benzotriazine with a variety of pyrrolidene enamine dienophiles. This last Diels-Alder example, although limited by modest yields, produced various 2,3-alkyl, carbocyclic-, and aryl-substituted, fully unsaturated quinolines based on the elimination of diatomic nitrogen, and the pyrrole (Scheme 42).¹²⁰

Scheme 42



Other examples of cycloaddition reactions forming quinolines include Parker's thermal 6π -electrocyclic annulation of vinyl quinone mono- and diimides. In these reactions, 6-amino and 6-hydroxyl-2-quinoline carboxylates are formed in good yields from readily-formed starting materials (Scheme 43). This sequence is particularly attractive in forming the 6-oxygenatedquinolines, since they appear in interesting natural product targets such as quinine (**5**), streptonigrin (**1**), and the luzopeptins.¹²¹

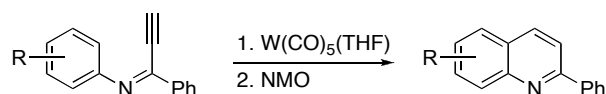
Scheme 43



Sangu's approach produced 2-arylquinolines by electrocyclization of alkynyl aryl imines catalyzed by 20 mol% $W(CO)_5(THF)$ in good yields, although the yield was dependent on the subsequent oxidation of the crude reaction mixture with 3 eq of

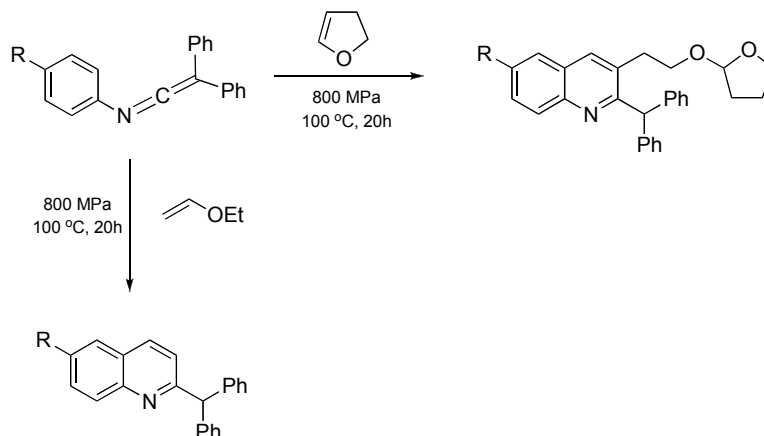
NMO (Scheme 44). This procedure was relatively tolerant of both electron-withdrawing and electron-donating groups on the aniline ring, as well as *ortho*- and *meta*-substituents, and, therefore, would be useful in generating a variety of substituted 2-arylquinolines.¹²²

Scheme 44



In the last cycloaddition example, Shimizu reported on the [4+2] cycloaddition of *N*-aryl substituted ketenimines with enol ethers. The reaction used several dihydrofurans to attack the *sp* carbon of the ketenimine group, which allowed the [4+2] cycloaddition to occur, leaving a furo-dihydroquinoline, which quickly rearranged to the 3-hydroxyethyl-2-benzylquinoline in good yields (Scheme 45).¹²³

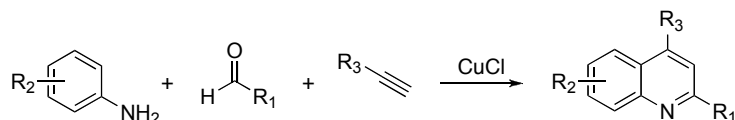
Scheme 45



MULTICOMPONENT REACTIONS

The last category of quinoline syntheses to report is that of multicomponent condensations. In 1995, Westerwelle reported the domino reaction of *N*-methyl anilinium perchlorate salts with 2 eq of a variety of alkyl aldehydes, which produced 2,3-alkyl-*N*-methyl quinolium perchlorates. The yield of this initially undesired product was optimized by the authors as much as possible by varying solvents, temperatures, and Lewis acids, with minimal improvement to the low to moderate yields.¹²⁴ In 2002, Syeda Huma reported the three-component reaction of aryl aldehydes, *p*-methoxyaniline, and terminal alkynes to produce 2-aryl-4-hydroxylalkyl-quinolines in modest yield (Scheme 46). This Cu(I)-catalyzed multicomponent reaction is expected to produce a combinatorial library of quinolines in an expeditious manner.¹²⁵

Scheme 46



CONCLUSION

A wide variety of approaches have been developed for the synthesis of the quinoline ring structure, including Skraup and Skraup-like techniques, Friedländer and Friedländer-like techniques, organometallic techniques, cycloadditions, and multicomponent reactions. Each of these methods has unique advantages and

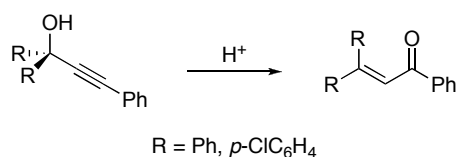
disadvantages. Some require unstable or synthetically challenging starting materials; others necessitate harsh reaction conditions. However none of those methods were specifically applicable to our desired retrosynthetic plan to produce streptonigrin.

Meyer-Schuster Rearrangement

HISTORY

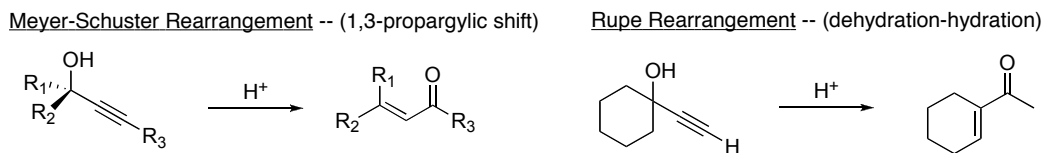
Meyer and Schuster first reported the acid-catalyzed rearrangement of propargyl alcohols to α,β -unsaturated ketones in 1922¹²⁶ (Scheme 47). They catalyzed their reactions with a variety of acidic systems, including acetic acid/sulfuric acid mixtures, dry HCl in ether, acetic anhydride and acetyl chloride.

Scheme 47



From that time until 1971 when Swaminathan and Narayanan wrote their review,¹²⁷ a myriad of acid-catalyzed examples were reported, as well as a few base-catalyzed examples for both the Meyer-Schuster (MS) rearrangement as well as the similar Rupe rearrangement (Scheme 48). That review also summarized the substrates capable of such rearrangements: (1) Rupe rearrangements were favored when an abstractable α -proton was available, while the MS rearrangement occurred when no such proton existed, and (2) the propensity for these types of rearrangement to occur followed a general carbocation stability pattern: primary α -acetylenic alcohols never rearranged, secondary alcohols did so only with additional stabilizing factors, and tertiary alcohols rearranged quite readily.

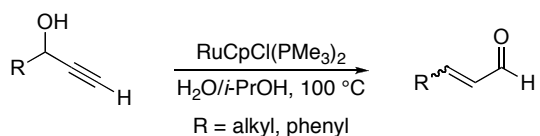
Scheme 48



The harsh acidic conditions used in those early reports of the Meyer-Schuster rearrangement led to a variety of by-products, mostly undesired, including competing rearrangements, methyl group migrations, and deoxygenations.¹²⁷ Since the 1970s, several transition metal catalytic systems have been identified to facilitate the MS rearrangement, yet none that are both mild and universally applicable. Early examples of transition metal catalysts employed titanium (IV) oxides,¹²⁸ vanadium (V) oxides,¹²⁹⁻¹³³ rhenium (VII) oxides¹³⁴ and molybdenum (IV) oxides.¹³⁵ These systems were only marginally less harsh, often requiring elevated temperatures and organic acids.

More recently developed catalysts have achieved the MS rearrangement under mild conditions, but each with their own drawbacks. In 2002, Suzuki reported the conversion of secondary propargyl alcohols to enals utilizing an aqueous cyclopentadienyl-ruthenium complex at 100 °C (Scheme 49). This system was particularly high-yielding for the examples given, yet is limited to secondary alcohols with terminal alkynes. Tertiary alcohols did not isomerize under these conditions.¹³⁶

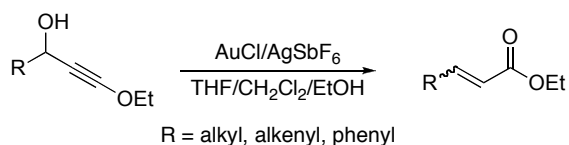
Scheme 49



Cadierno also utilized a ruthenium complex to catalyze both the MS and Rupe rearrangements. His (η^3 -allyl)-ruthenium(II) complex was capable of isomerizing both secondary and tertiary propargyl alcohols, however was limited to terminal alkynes in a manner similar to Suzuki's work due to the vinylidene-ruthenium mechanistic pathway of the reaction.^{137,138}

Examples of metal-catalyzed MS rearrangements of internal alkynes have also been recently reported. Sugawara achieved silver(I)-catalyzed, carbon dioxide-mediated MS rearrangements of tertiary propargyl alcohols in excellent yield.¹³⁹ Imagawa also reported the rearrangement of primary propargyl acetates to enones using $\text{Hg}(\text{OTf})_2$ in aqueous acetonitrile.¹⁴⁰ However, the most interesting recent reports of metal-catalyzed MS rearrangement have come out of the Dudley research group at Florida State University. Using gold catalysts (AuCl_3 and AuCl-AgSbF_6), Dudley achieved MS rearrangement of both tertiary and secondary propargyl alcohols into α,β -unsaturated ketones and enoates (Scheme 50).^{141,142}

Scheme 50

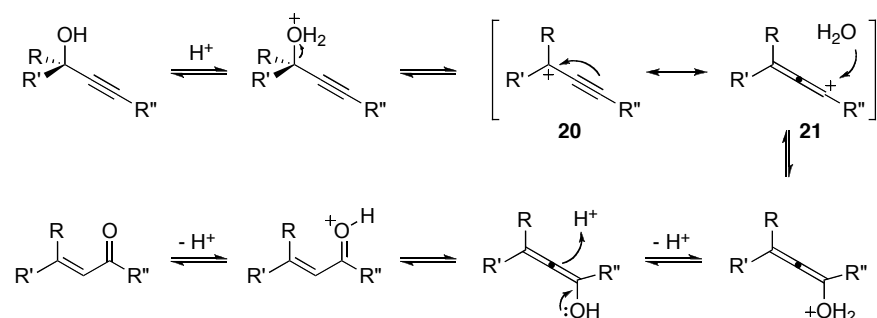


MECHANISTIC STUDIES

Early investigations of the MS rearrangement concluded that elimination of the protonated hydroxyl group resulted in an alkynyl cation (**20**), which would be in resonance with an allenyl cation (**21**) (Scheme 51). That cationic species was

reportedly stable enough, with a half-life of 45 min at 25 °C in conc. H₂SO₄, to be detected by NMR and UV spectroscopy.¹⁴³

Scheme 51



In 1977, Edens published kinetic studies of the MS rearrangement.¹⁴⁴ Using a combination of Hammett analysis of substituent effects and solvent isotope effects, Edens concluded from the substituent effects data that the transition state has definite cationic character, and has substantial charge delocalized from the reaction center to the rearrangement terminus. Also, from the inverse α -secondary isotope effect observed, Edens concluded that the rate-limiting step involves a partial rehybridization ($sp \rightarrow sp^2$), implying covalent attachment at the rearrangement terminus. However, Edens' data could not distinguish between an intramolecular shift of the oxygen versus a bimolecular process involving nucleophilic attack by water (Figure 5).

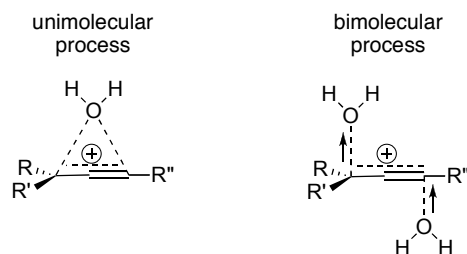


Figure 5. Eden's Proposed Transition State Models

Computational studies have also been reported with regard to the mechanism of the MS rearrangement.¹⁴⁵⁻¹⁴⁷ The most recent report of density functional theory calculations by Yamabe concludes that (1) the MS rearrangement is indeed a bimolecular process, and (2) transition state geometries are carbonium-ion like, with the C-O bond length of the departing oxygen at 2.71Å, and that of the attacking oxygen at 2.27Å (Figure 6).

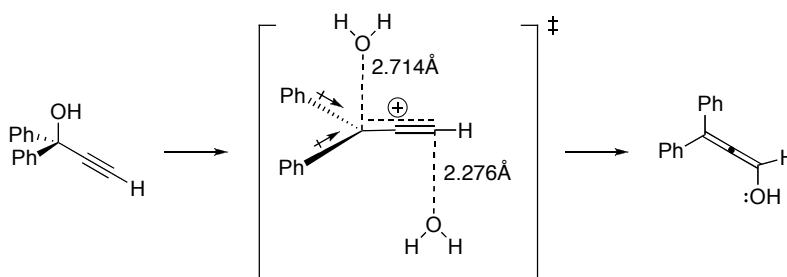


Figure 6. Yamabe Transition State Model for MS rearrangement of 1,1-diphenylprop-2-yn-1-ol.

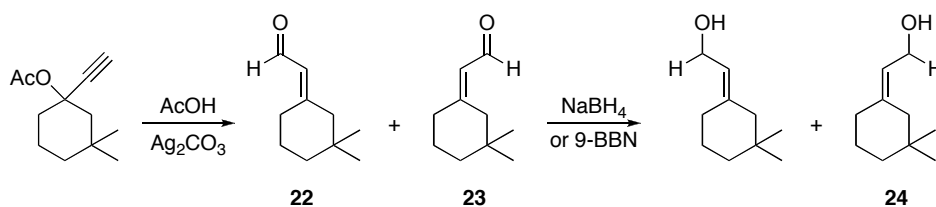
This latter result was contrary to their calculations for the Rupe rearrangement, which showed almost identical bond lengths for the departing and attacking oxygens. Yamabe attributed this difference to the carbocationic charge stabilization by the two adjacent phenyl rings in their model, which implies that the MS rearrangement (more

so than the Rupe) requires electron-donating groups to facilitate the isomerization from propargyl alcohol to allenol. Yamabe also highlighted the difference in activation energy calculated for the rearrangement of 1,1-dimethylprop-2-yn-1-ol ($\Delta E^\ddagger = 29.92$ kcal/mol) and 1,1-diphenylprop-2-yn-1-ol, ($\Delta E^\ddagger = 13.42$ kcal/mol) as further evidence of the role of the phenyl groups in stabilizing the carbocationic nature of the transition state.

APPLICATIONS

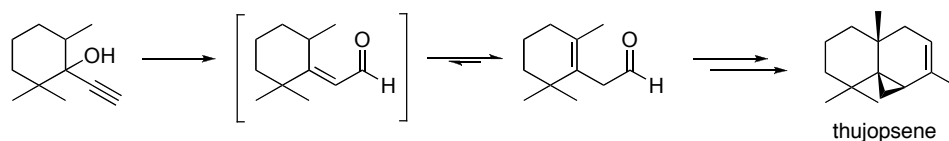
Although heavily studied both methodologically and mechanistically, application of the MS rearrangement is less commonly identified in the literature. An early example was reported by Pelletier in his synthesis of three monoterpene pheromones (**22**, **23**, and **24**, Scheme 52) of the male boll weevil *Anthonomus grandis* Boheman in 1976. The rearrangement of the acetate of 1-ethynyl-3,3-dimethylcyclohexanol was not stereoselective, resulting in a 47:53 mixture of the two desired aldehydes in high (88-90%) yield. Those aldehydes could be further reduced to produce a mixture of the corresponding *Z/E* alcohols, of which the *Z* alcohol (**24**) was one of their desired products.¹⁴⁸

Scheme 52



Amos Smith also utilized tris(triphenylsiloxy) vanadate to catalyze a MS rearrangement enroute to his total synthesis of three members of the thujopsene class of sesquiterpenes: (\pm)-mayurone, (\pm)-thujopsene and (\pm)-thujopsadiene (Scheme 53).¹⁴⁹

Scheme 53



Lastly, two more recent examples of the application of the MS rearrangement in natural product synthesis include the work by Crich on the AB-ring system of taxol¹⁵⁰ and the synthesis of novel histamine H₃-receptor antagonists by Stark *et al.*¹⁵¹

Despite the wealth of studies on the various types of acid and transition metal catalysts capable of facilitating this rearrangement, and several theoretical studies on its precise mechanism, application of the Meyer-Schuster rearrangement in synthesis has been relative rare. However, its potential role in the quinoline heteroannulation to be described in later chapters makes it a vital element in this research.

Streptonigrin

BACKGROUND

Streptonigrin (**1**) is an aminoquinone antibiotic with significant antitumor, antiviral and antimicrobial activity. Since its isolation by Rao and Cullen from *Streptomyces flocculus* in 1959, streptonigrin has been thoroughly studied, both chemically and medicinally (*vide infra*). Despite its effectiveness as a chemotherapy agent for a variety of cancers (breast, lung, head, neck, lymphoma and melanoma),¹⁵² streptonigrin displayed deleterious side effects, including bone marrow depression, and clinical trials were abandoned in 1977. Since that time, a body of work has been undertaken to identify the mechanisms of both its anti-neoplastic activity as well as its clastogenic activity. The primary goal of these studies was to identify streptonigrin's active pharmacophore, allowing the rational design of an analogue that would modulate the clastogenic activity while maintaining the anti-neoplastic effects. To date, streptonigrin's fully-functionalized tetracyclic structure has successfully synthesized by only three research groups,¹⁵³⁻¹⁵⁵ although many other efforts have been reported toward segments of the streptonigrin structure. Those lengthy total syntheses, however elegant, would not be commercially viable for the production of streptonigrin, or any newly identified, efficacious analogue. In that regard, a new efficient, versatile synthesis of streptonigrin is sought in this research project.

MODE OF ACTION / PHARMACEUTICAL VALUE

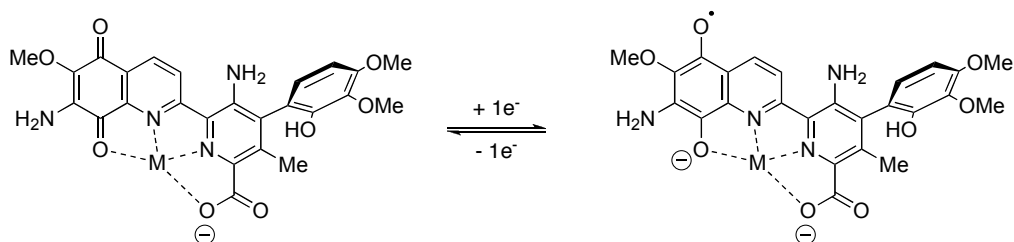
Streptonigrin has long been known to have an array of cytotoxic and genotoxic effects. Its cytotoxicity has been linked to depletion of NADPH/NADH, the uncoupling of oxidative phosphorylation, leading to observable depletion of cellular ATP, as well as severe DNA degradation. The numerous investigations on the impact of streptonigrin on DNA have been thoroughly reviewed in a recent report by Bolzán and Bianchi.¹⁵² That report summarized streptonigrin's unique activity both as a radiomimetic compound, damaging chromosomes in an S-independent manner, as well as causing G₁-phase chromatid-type aberrations and sister-chromatid exchanges typical of S-dependent agents. Streptonigrin binds irreversibly to minor groove of DNA, and its clastogenic effects have been shown to be persistent long after exposure.

Streptonigrin has been shown *in vitro* to be reduced by a one or two-electron process, producing semiquinone radicals or hydroquinone, respectively. Either species is capable, through Fenton-type reactions to produce superoxide radicals and hydroxyl radicals capable of damaging DNA. Once bound to DNA, this cyclical process can cause chromosomal aberrations in nanomolar concentrations, and such damage can persist through multiple cell cycles.¹⁵⁶ The role of those active oxygen species was indirectly demonstrated by the addition of liposome-encapsulated antioxidant enzymes superoxide dismutase and catalase, as well as the hydroxyl radical scavenger mannitol, to Chinese Hamster ovary (CHO) cells, which significantly lowered the observed chromosomal aberrations.

Similarly, the role of metal ions in streptonigrin-mediated DNA damage has been evidenced by the addition of metal chelating compounds such as desferrioxamine, 2,2-dipyridyl and 1,10-phenanthroline to streptonigrin-exposed cell lines. In each case, the chelators significantly inhibited the induction of chromosomal aberrations.¹⁵²

One particularly interesting study by Harding's group from the University of Sydney highlights the continued interest in identifying the role of *d*-block metal ions in the redox chemistry of streptonigrin-mediated DNA damage.¹⁵⁷ The redox potentials of the quinone in streptonigrin were studied by cyclic voltammetry (CV) in the presence of varied concentrations of metals (Cd(II), Fe(II), Zn(II), Co(II), Mn(II) and Ni(II)). Harding observed a reversible single-electron reduction in the presence of metal ions (Scheme 54), which occurred at a more positive potential (more easily reduced) than free streptonigrin solutions.

Scheme 54



The same CV experiments were also performed on two AB-ring segments of streptonigrin (with and without the 7-amino group, no CD ring component). The observed quinone redox potentials were also positively shifted in the presence of the metal ions, however the magnitude of that shift was significantly more than for streptonigrin. Harding hypothesized that without any C-ring coordination, metal

coordination to the quinone oxygen would be greater, impacting the redox potentials. However, streptonigrin's metal coordination would be influenced by the C-ring pyridyl nitrogen as well as the carboxylate, limiting the impact on the quinone system.

This hypothesis agreed with past studies attempting to identify the active pharmacophore of streptonigrin.¹⁵⁸ Boger synthesized a broad spectrum of AB-ring segments, CD-ring segments, and ABC-ring analogues, systematically excluding components of the proposed streptonigrin-metal complex. Boger tested these analogues for antimicrobial and cytotoxicity, and found that:

- (1) the fully functionalized CD-ring alone was biologically inactive;
- (2) the AB-ring 6-methoxy group was relatively unimportant;
- (3) the C-ring pyridyl nitrogen was extremely important (it's carbocyclic analogue was significantly less active;
- (4) the role of the C-ring free carboxylate was ambiguous, fully functionalized streptonigrin was much more active than its methyl ester derivative, but smaller ABC-ring segments displayed the opposite trend of activity.

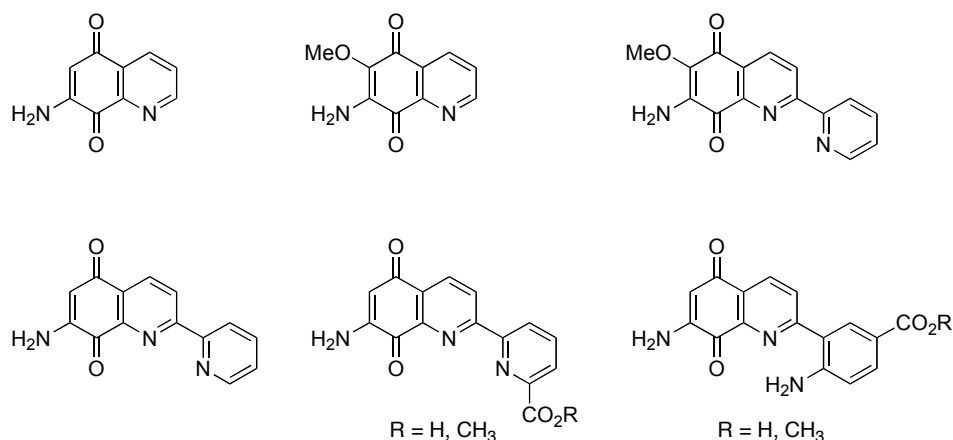
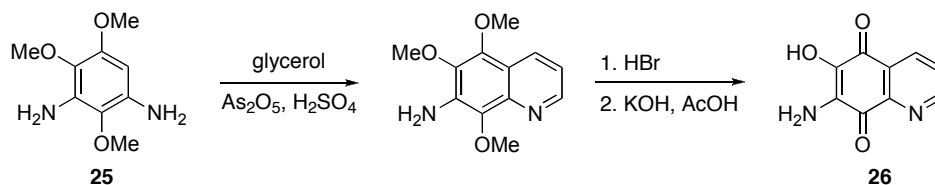


Figure 7. Boger's Streptonigrin Analogues to Determine the Active Pharmacophore

Previous AB-Ring Syntheses

The past efforts toward the synthesis of the quinoline-5,8-quinone AB-ring of streptonigrin have been focused on utilizing the known quinoline syntheses discussed earlier. The earliest example was developed by Kametani, using a classical Skraup reaction of diamino-trimethoxybenzene **25** (Scheme 55),⁴ which after oxidation, formed the desired 7-amino-6-hydroxyquinoline-5,8-quinone **26**.

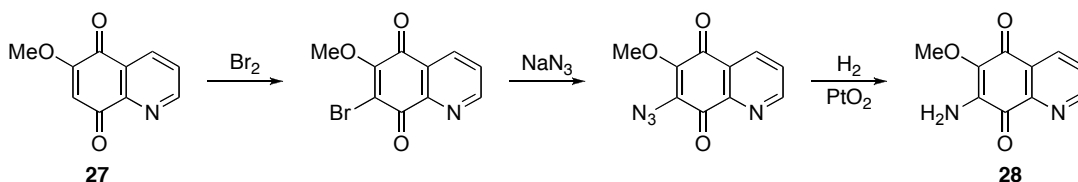
Scheme 55



A similar Skraup synthesis route was taken by Cheng¹⁵⁹ to form 6-methoxyquinone **27**. This quinone was further functionalized to introduce the 7-amino group via a three-step process: bromination of the quinone, substitution by

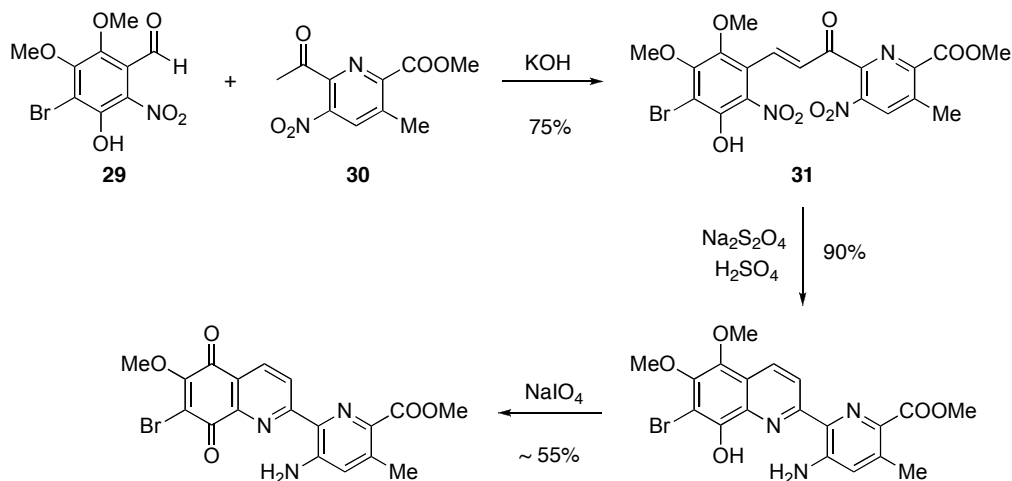
azide, and reduction to form the 7-amino-6-methoxyquinoline-5,8-quinone **28** (Scheme 56). This strategy was later successfully used in both Weinreb and Kende's total syntheses of streptonigrin.

Scheme 56



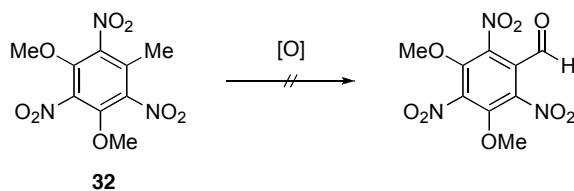
In 1979, Rao reported the synthesis of ABC-ring segments of streptonigrin via a two-step Friedländer approach,¹⁶⁰ condensing acetylpyridine **30** with nitrobenzaldehyde **29** to form the nitrochalcone **31**. Reductive cyclization of chalcone **31** with sodium dithionite produced the desired quinoline in excellent yield. Subsequent oxidation to the quinolinequinone was complicated by the partial formation of a dimethyl acetal byproduct, which after separation could be cleaved with acid to produce the quinone in a combined yield of 55%. Rao also utilized the aforementioned method by Cheng to introduce the final 7-amino function.

Scheme 57



In that same report, Rao also made an interesting hypothesis, proposing that the 2,4,6-trinitro-3,5-dimethoxytoluene **32** would make a simple, yet ideal A-ring precursor for the same two-step Friedländer approach. Despite its potential as an explosive, he synthesized **32** on a relatively large scale (13g), yet reported he could find no appropriate oxidation conditions to transform the toluene methyl group into an aldehyde (Scheme 58). Oxidation of compounds similar to **32** would later be investigated as part of our approach to an A-ring precursor.

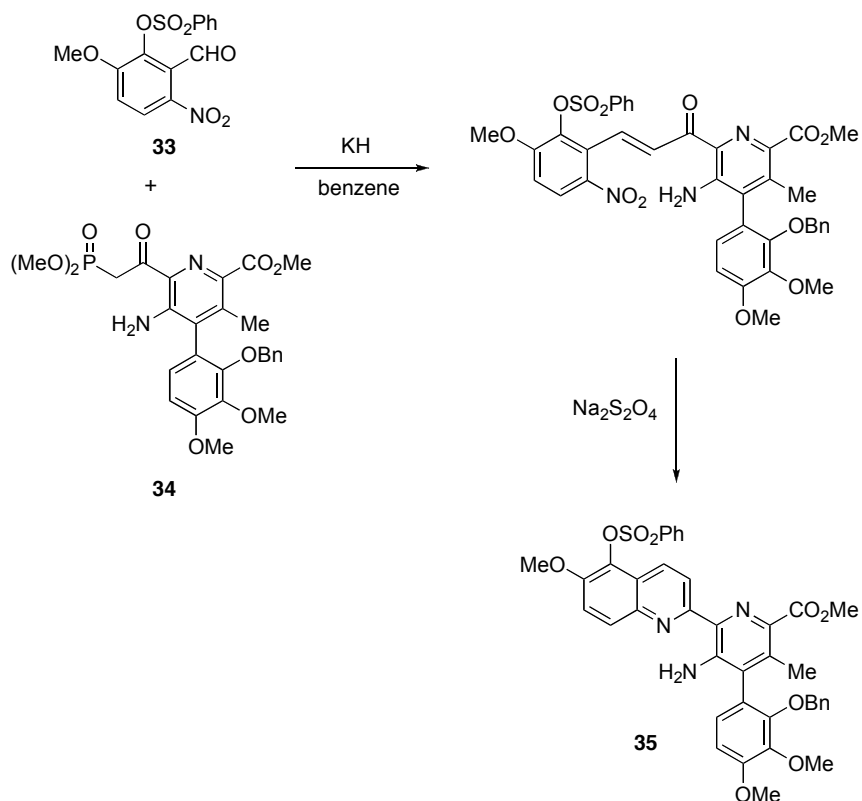
Scheme 58



THE WEINREB SYNTHESIS

Weinreb utilized many interesting transformations to complete the first total synthesis of streptonigrin,¹⁵³ including an imino Diels-Alder reaction to form the C-ring pyridine. However, this discussion will focus on his specific approach toward the AB-ring system. Preliminary efforts toward the AB-ring by Weinreb identified a modified Friedländer approach, utilizing a Wadsworth-Emmons-Horner condensation of β -ketophosphonate **34** with a nitrobenzaldehyde **33** to successfully form the desired nitrochalcone in 80% yield. This nitrochalcone was reduced with sodium dithionite, cyclizing to form the pyridylquinoline **35** in 60% yield (Scheme 59). This sequence was quite effective, however four steps were required to build the β -ketophosphonate **34** from his last CD-ring intermediate, with a 41% overall yield. In addition, nitrobenzaldehyde **33** was merely referenced as a known compound, but the effort required to produce it was not included. Overall, Weinreb's work to produce synthetic streptonigrin, although elegant and certainly timely, required 32 linear steps with an overall yield of approximately 0.036% from his D-ring precursor.

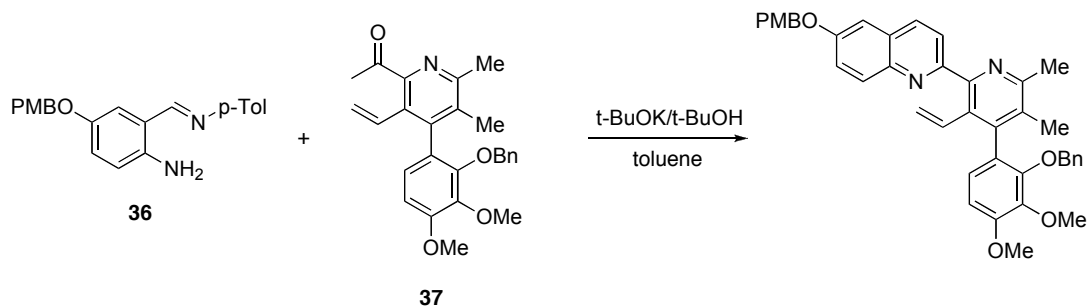
Scheme 59



THE KENDE SYNTHESIS

In a manner similar to that of Weinreb, Kende chose to construct streptonigrin from the D-ring “north”. However, to assemble the AB-ring, Kende chose a Borsche reaction to form the heterocyclic B-ring. He arrived at a 2-chloropyridine CD-ring intermediate which could be modified in 2 steps (70% yield) to his Borsche adduct 2-acetylpyridine intermediate **37**. Kende’s A-ring precursor, iminoaniline **36**, was prepared in three steps (60%) from the known compound 5-hydroxy-2-nitrobenzaldehyde. The commercial availability of such aldehyde at that time is unknown. The subsequent Borsche reaction was quite fruitful, producing the tetracyclic product in 90-96% yield. Kende’s total synthesis of streptonigrin required 23 steps, with an overall yield of ~ 0.13%, from his D-ring precursor.¹⁵⁴

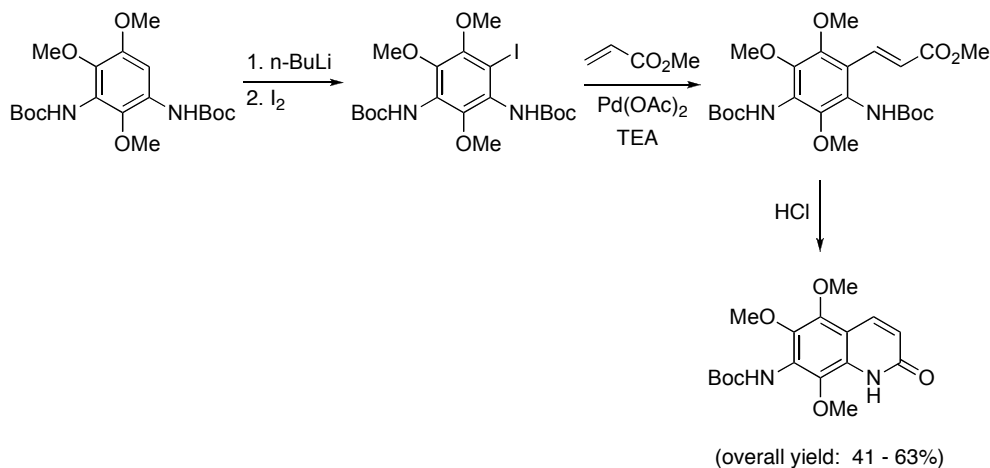
Scheme 60



RECENT AB RING SYNTHESSES

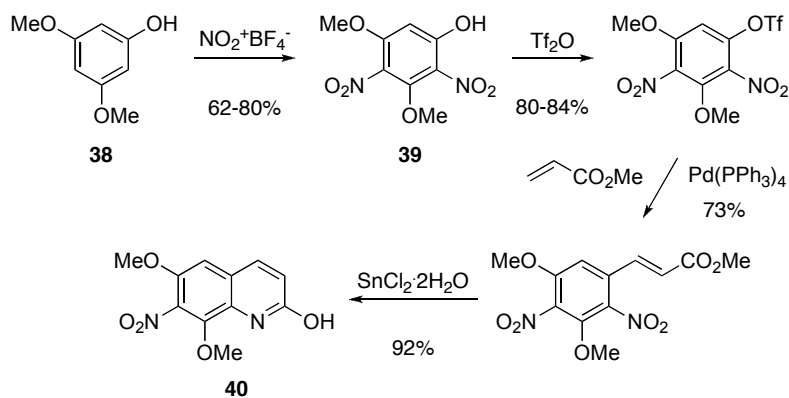
More recent efforts at heteroannulation of the AB-ring system of streptonigrin have utilized Heck coupling approaches to form the 3-carbon segment required for assembling the B-ring. In an on-going effort by Quéguiner, a series of 2-quinolones were produced, one with the proper A-ring functionality, by a sequence of *ortho*-directed metalation, iodination, Heck coupling with methyl acrylate and acid-catalyzed cyclization (Scheme 61).¹⁶¹ This process, however high yielding, results in a quinolone that is converted in 2 steps to a 2-quinolyltrimethylstannane, for subsequent Stille coupling to a 2-pyridyl triflate CD-ring analogue. No pharmaceutical-friendly palladium-catalyzed aryl-aryl coupling reactions have successfully formed the 2-quinolyl-2'-pyridyl bond required for streptonigrin.

Scheme 61



A recent report by Holzapfel and Dwyer also utilizes a Heck coupling to form the AB-ring system (Scheme 62).¹⁶² Dinitration of dimethoxyphenol **38** with nitronium tetrafluoroborate formed the dinitrophenol **39** in good yield (no regioselectivity issues were addressed). Treatment with triflic anhydride generated the aryl triflate needed for Heck coupling. Reductive cyclization afforded 2-hydroxyquinoline in excellent yield. In a manner similar to Quéguiner, Holzapfel planned to convert **40** to 2-quinolyl triflates and utilized Stille coupling with 2-pyridyltrimethylstannanes to form the ABC-ring system.

Scheme 62



The aforementioned efforts to form the AB-ring system, although successful in their own right, were not sufficient for our planned synthesis of streptonigrin. Whether hampered by long lead-in steps, undesired organostannane coupling reagents, or omitted A-ring functionality that would be added post-cyclization, these precedents would not meet our goal of utilizing McElroy's CD-ring pyridyl triflate **2** (Figure 1) in a mild, yet efficient, manner. A new quinoline synthesis was required that would couple to **2** using mild, non-toxic organometallic reagents, produce the AB-ring with minimal post-cyclization modifications, and do so in a convergent manner that would allow the greatest flexibility in producing analogues that may be screened in the future for enhanced antitumor activity.

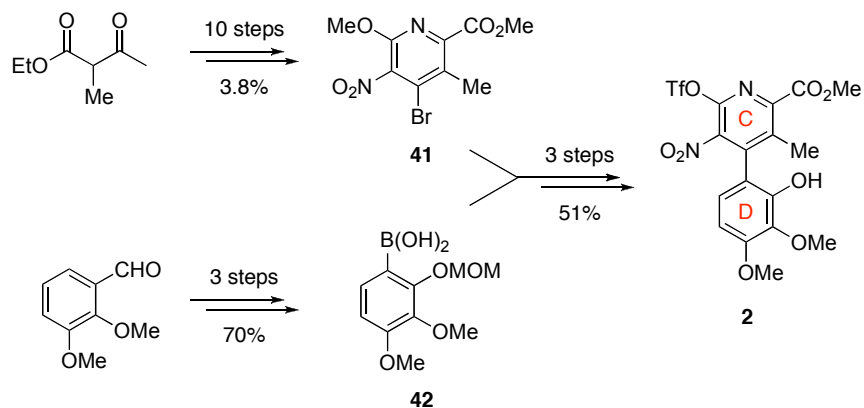
Results and Discussion

Tandem Reduction/Cyclization of o-Nitrophenyl Propargyl Alcohols

AB RING MODEL SYSTEMS

In our on-going efforts to synthesize streptonigrin (**1**),² (Scheme 64)¹ McElroy developed an efficient route to the functionalized, protected CD pyridyl triflate **2**. This convergent approach produced the highly functionalized C ring intermediate bromopyridine **41** in a 10-step sequence, and the requisite D-ring boronic acid **42** in 3 steps. Following successful Suzuki coupling of these arenes, the 2-methoxy group was converted to triflate in two steps, generating the CD-ring intermediate pyridyl triflate **2** in an overall yield of ~ 2 % across the longest, 13-step linear sequence.

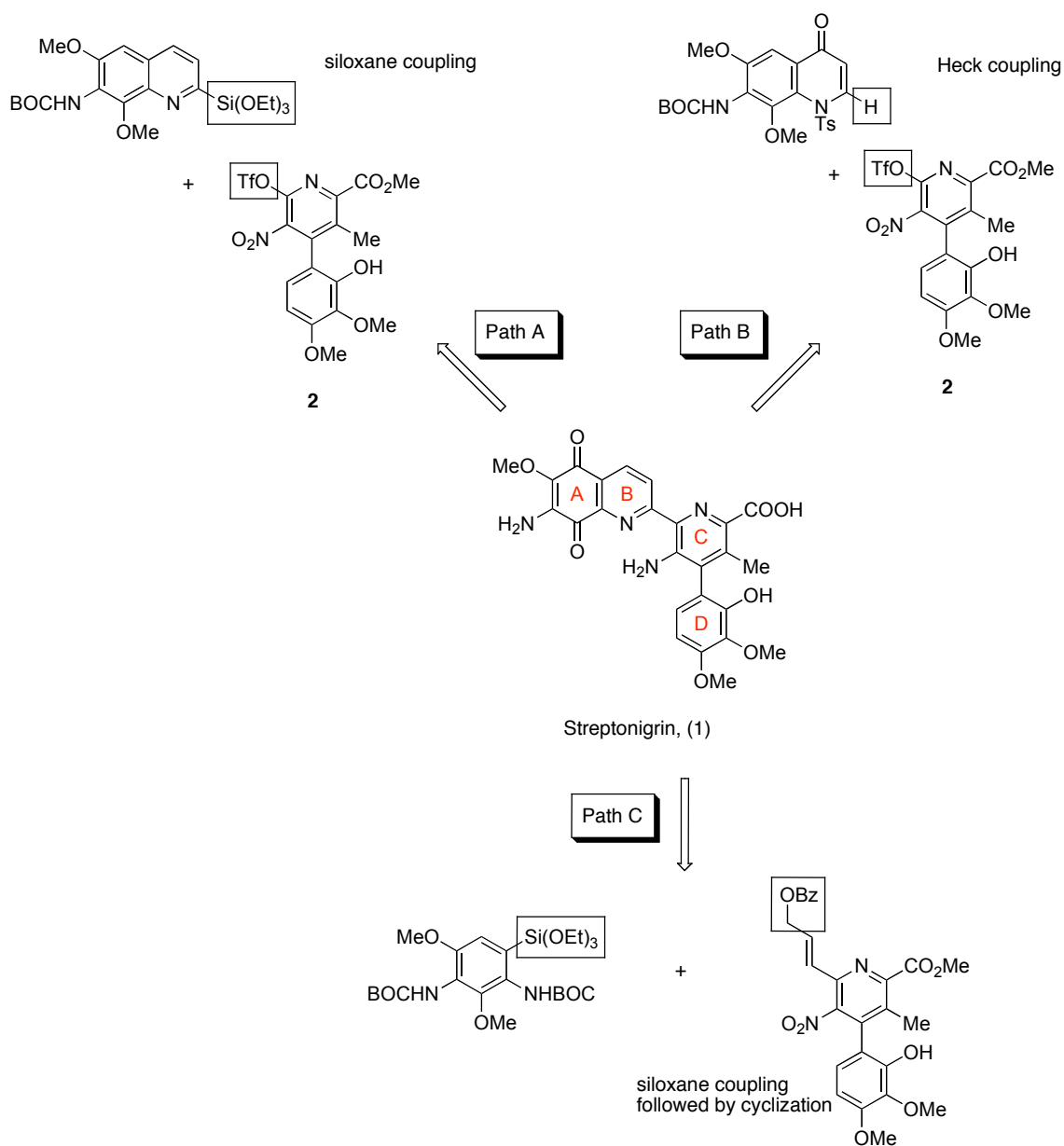
Scheme 63



McElroy also investigated routes to couple that intermediate to preassembled AB ring precursors (Scheme 64, Paths A & B), or an A ring precursor with a subsequent B ring cyclization (Path C). Although limited in breadth, there are several literature

precedents for forming 2-(2'-pyridyl)quinolines via organometallic cross-coupling reactions,¹⁶³⁻¹⁶⁹ supporting the potential of McElroy's retrosynthesis (Path A).

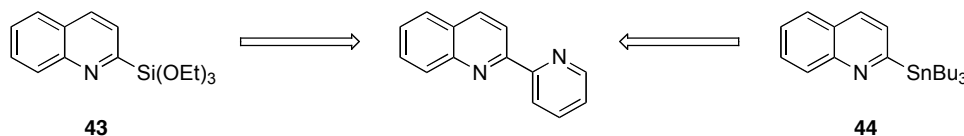
Scheme 64



McElroy investigated a model system for pathway A. The synthesis of the quinoline siloxane **43** (Scheme 65) from 2-bromoquinoline, by either hydrosilylation or lithium halogen exchange, followed by quenching with Si(OEt)₄, was

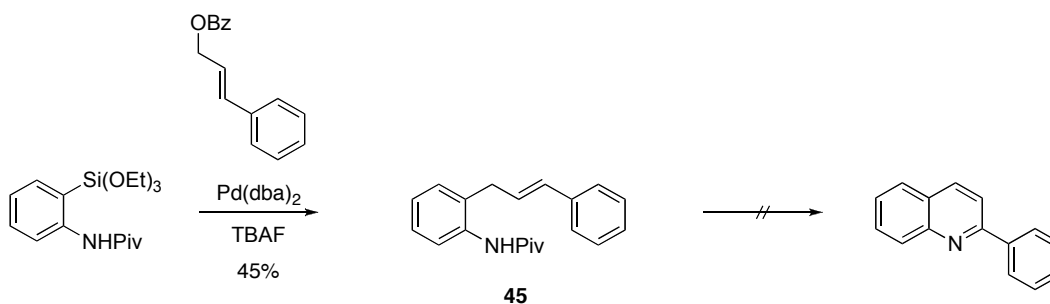
unsuccessful, and gave only low yields of the desired siloxane. The analogous quinoline stannane **44** was generated in modest yield, but Stille coupling attempts with 2-pyridyl triflate yielded none of the desired biaryl product. In addition, both siloxane **43** and stannane **44** were unstable, and protodemetallated on standing leaving quinoline.¹

Scheme 65



The cross coupling of aryl siloxanes and allylic benzoates required for Path C was studied in a model system, and produced moderate yields of the desired olefin **45** (Scheme 66). However, intramolecular amination attempts produced 2-phenylquinoline in very low yield.

Scheme 66



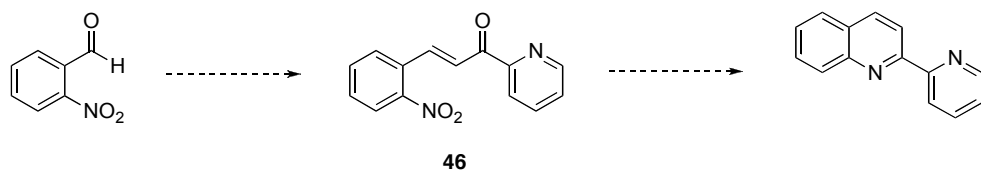
Since McElroy's work exhausted the siloxane aryl-aryl and aryl-allyl coupling possibilities, we needed to develop a new retrosynthetic path, preferably one with a mild cross-coupling step that took full advantage of the readily available CD intermediate **2**. We focused on coupling triflate **2** to an A ring precursor and forming

the heterocyclic B ring subsequently. Success in that regard would require a new quinoline-forming technique.

The development of a new quinoline synthesis (Scheme 67) to meet our needs started with the well-precedented transformation of nitrochalcones **46** to quinoline by reduction of the nitro group followed by ring closure and aromatization.^{102-104,106,170-}

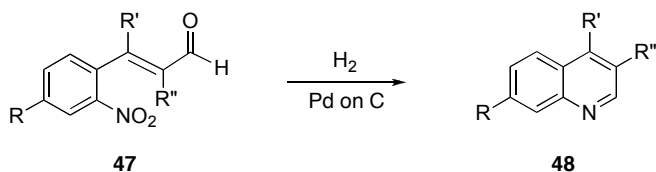
173

Scheme 67



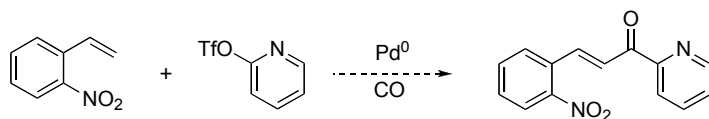
In one such example, Banwell and coworkers¹⁰⁶ reduced the nitro groups of (*Z*)- β -nitroaryl-enals **47** to form a series of 2,3-substituted quinolines **48** in good to excellent yields (Scheme 68). Where our synthetic plan diverged was in the preparation of those nitrochalcones.

Scheme 68



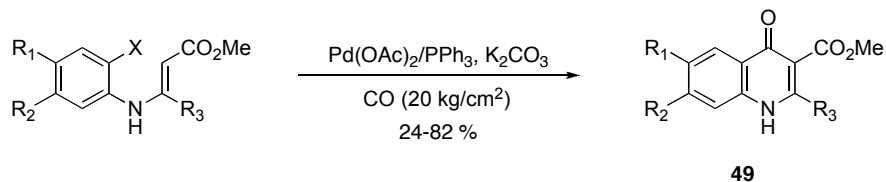
Our first plan to produce the pyridyl nitrochalcone **46** centered around a proposed carbonylative Heck reaction (Scheme 69). Oxidative addition of palladium into the pyridyl-triflate bond, followed by carbon monoxide insertion, alkene insertion, and β -hydride elimination would produce the desired enone.

Scheme 69



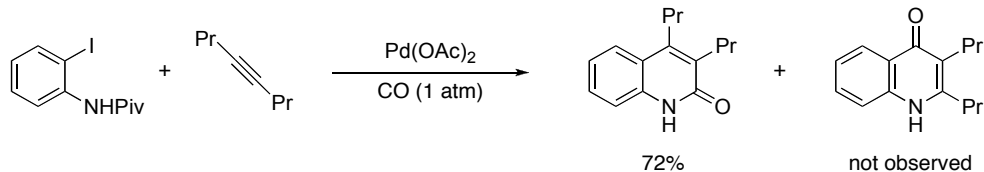
However, atmospheric pressure carbonylative Heck reactions normally proceed with alkene migration first, followed by insertion of the carbon monoxide,¹⁷⁴ forming an acyl palladium species. High pressure carbonylative Heck reactions have been used to generate quinolones **49** (Scheme 70).¹⁷⁵ Attempts by Torii and coworkers to conduct this reaction under low pressure produced Heck coupling only, without carbonyl insertion.

Scheme 70



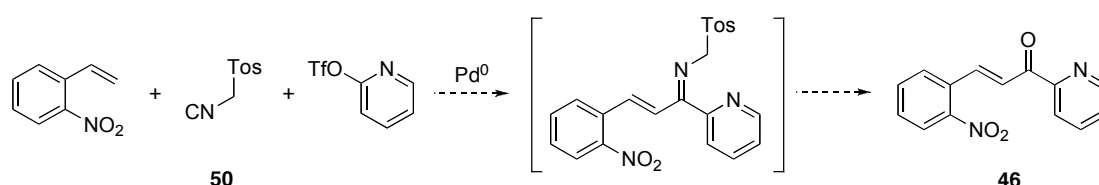
Analogous processes using terminal alkynes have been thoroughly studied by Larock,^{176,177} demonstrating that high pressures are required to force carbon monoxide insertion to occur before the alkyne insertion. Under low-pressure conditions, carbonyl insertion occurred after alkyne insertion (Scheme 71).

Scheme 71



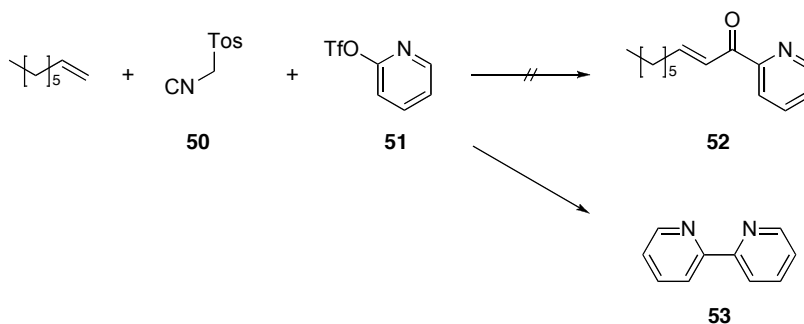
In order to develop a novel, practical approach, circumventing the need for high-pressure, we envisioned a carbonylation using a solid isocyanide **50** as the carbon monoxide synthon (Scheme 72).¹⁷⁸ Isocyanides are isoelectronic with carbon monoxide, and are known to insert into palladium-carbon σ -bonds in a similar manner,¹⁷⁹⁻¹⁸³ however we could find no synthetic application of such an insertion reported in the literature.

Scheme 72



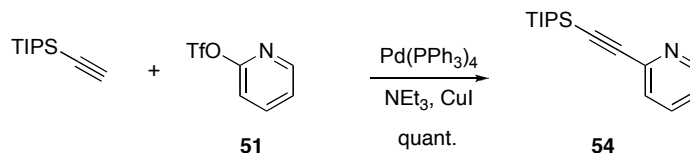
Several catalyst/base/additive combinations were surveyed as potential conditions for the model transformation with 1-octene: using Pd/C or $\text{Pd(PPh}_3)_4$ as catalysts, with either potassium carbonate or triethylamine bases, with and without lithium chloride additives. Unfortunately, no pyridyl enone **52** was observed under any of these conditions (Scheme 73). Removal of the isocyanide **50**, and simply attempting the Heck reaction alone on 2-pyridyl triflate **51** with 1-octene produced no cross-coupled product. The only coupling observed under these conditions was homocoupling, producing 2,2'-bipyridine **53**. Accordingly, this approach to the synthesis of quinoline was abandoned.

Scheme 73



Next we chose to examine the potential of a Sonogashira coupling using our 2-pyridyl triflate CD ring intermediate. This reaction was modeled using commercially available 2-pyridyl triflate **51** and TIPS-acetylene (Scheme 74). Under standard Sonogashira conditions, using 2 mol% tetrakis(triphenylphosphine) palladium, copper iodide and excess triethylamine, the reaction produced TIPS-pyridyl acetylene **54** with a quantitative conversion and no bipyridine was observed.

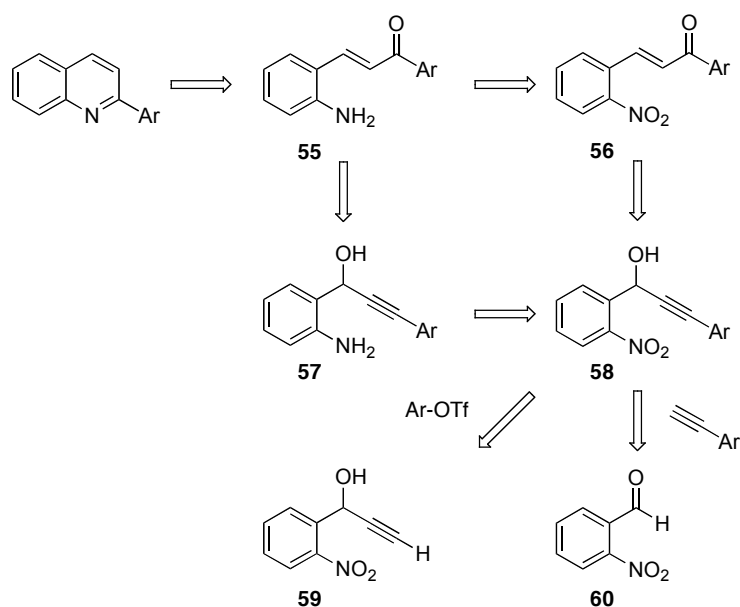
Scheme 74



This result led us to devise a new route to our desired pyridylnitrochalcone (Scheme 75). Starting from readily available *o*-nitrobenzaldehyde **60**, adding an acetylene unit to make the secondary propargyl alcohol **59**. This alcohol could be coupled using Sonogashira conditions to the CD ring pyridyl triflate. The resulting pyridyl propargyl alcohol **58** could be transformed into the required *o*-aminochalcone **55** by either reduction first, then rearrangement (**58**→**57**→**55**), or Meyer-Schuster

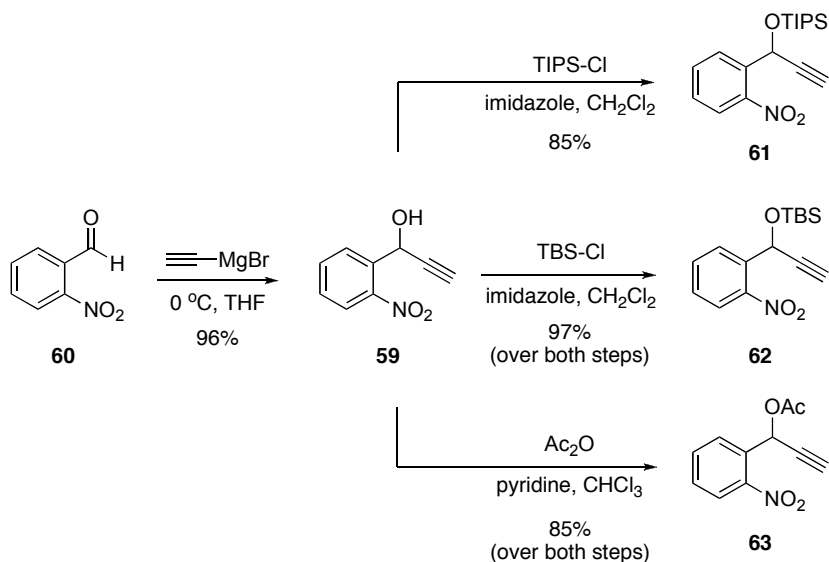
rearrangement could be performed on the *o*-nitrophenyl propargyl alcohol, generating the *o*-nitrochalcone, followed by reduction (**58**→**56**→**55**).

Scheme 75



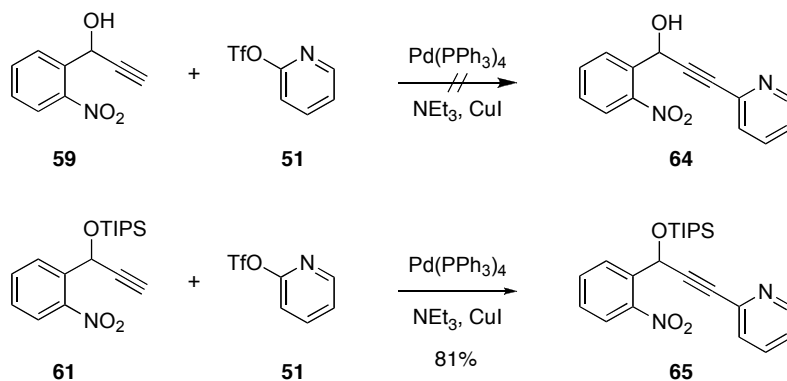
Testing this approach, ethynylmagnesium bromide reacted with *o*-nitrobenzaldehyde **60** to form the terminal secondary propargyl alcohol **59** (96%). Anticipating the hydroxyl group would require protection for the upcoming Sonogashira coupling, we prepared three protected derivatives **61-63** (Scheme 76).

Scheme 76



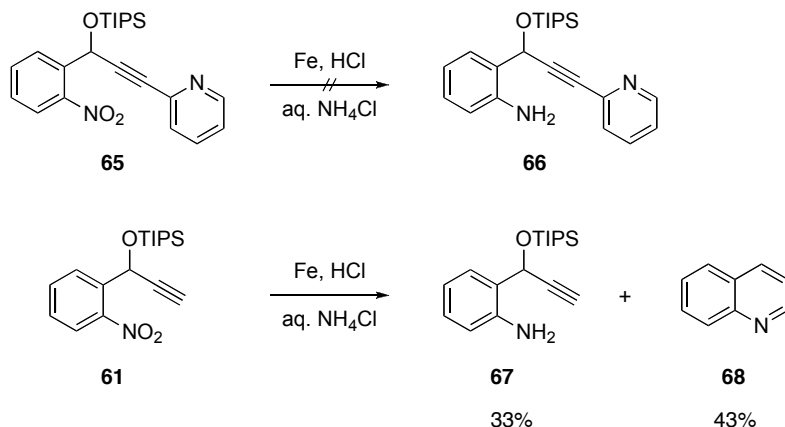
With a variety of propargyl alcohols in hand, we investigated the Sonogashira reaction of pyridyl triflate **51**. Although our previous assumption appeared to be correct, and the unprotected propargyl alcohol **59** did not couple, the TIPS-protected **61** coupled well (Scheme 77). Stirred at room temperature, with 2 mol% tetrakis(triphenylphosphine) palladium, copper iodide and triethylamine, the desired TIPS-protected pyridyl propargyl alcohol **65** was produced in 81% yield.

Scheme 77



We anticipated that reduction of the nitro group would increase the electron density of the phenyl ring, hopefully facilitating the Meyer-Schuster rearrangement. Therefore, pyridyl propargyl alcohol **65** was subjected to nitroarene reduction conditions¹⁸⁴ (Scheme 78). Iron metal stirred in ethanol with aqueous HCl and aqueous ammonium chloride produced none of the intended aniline **66**. Instead, a complex reaction mixture was obtained, the products of which would be identified later. However, when terminal alkyne **61** was subjected to the same reducing conditions, we observed a dramatically different, and immediately clear result. Reduction of **61** produced a mixture of the expected aniline **67**, in 33% yield, and quinoline **68** in 43% yield.

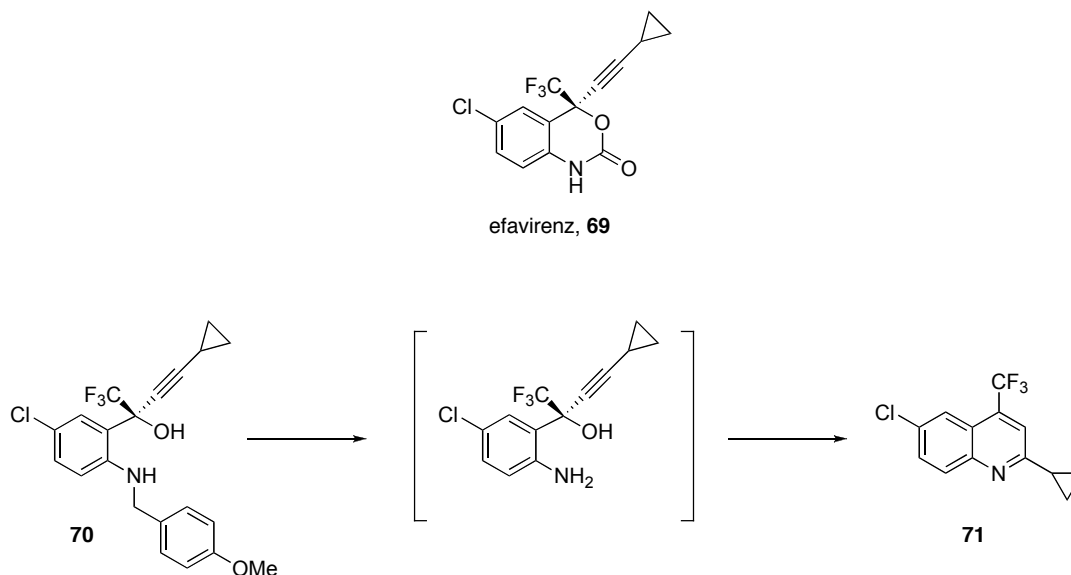
Scheme 78



Although the pyridyl-substituted example did not yield quinoline under reducing conditions, the fortuitous direct conversion of the *o*-nitrophenyl propargyl alcohols to quinoline in one pot deserved further examination. A thorough literature search identified a single example of such an observation. In the synthesis of DuPont's

HIV-1 non-nucleoside reverse transcriptase inhibitor efavirenz **69** (brand name SUSTIVA[®]), Choudhury and coworkers observed that many of their PMB deprotection schemes for tertiary propargyl alcohol **70** led to substantial, irreversible conversion to quinoline **71** (Scheme 79).¹⁸⁵

Scheme 79

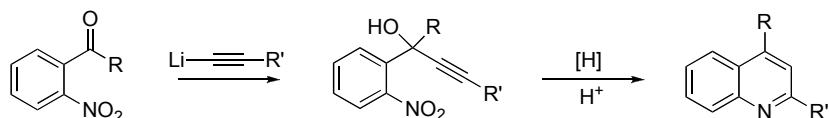


We were intrigued by Choudhury's observation—although an undesired by-product in DuPont's synthesis—of the mild conversion of *o*-anilino-propargyl alcohols to quinolines, potentially through an acid-catalyzed Meyer-Schuster rearrangement. This appeared to be an exploitable avenue to achieve our desired goal.

We developed a plan (Scheme 80) to study this transformation, starting from readily available *o*-nitrobenzaldehyde and 2'-nitroacetophenone. The addition of a variety of lithium acetylides was used to form the desired *o*-nitrophenyl propargyl

alcohols, and after reduction of the nitro group, we examined the quinoline-forming potential of these derivatives.

Scheme 80



Since Choudhury's system involved tertiary propargyl alcohols, initial testing was done adding the lithium acetylides of 1-hexyne and phenylacetylene to *o*-nitroacetophenone, generating the propargyl alcohols **38** and **39**, respectively (Table 1). A series of common nitroarene reducing conditions was tested, including Fe/HCl,¹⁸⁴ Zn/NH₄Cl,¹⁸⁶ TiCl₃/HCl¹⁸⁷ and SnCl₂/HCl.¹⁸⁸ With the exception of TiCl₃/HCl, each of the reduction conditions produced 2-butyl-4-methylquinoline **40** and 4-methyl-2-phenylquinoline **41** in excellent yields.

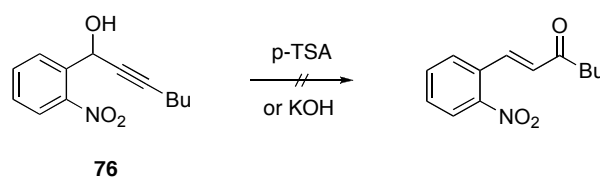
Table 1. Comparison of Reduction Conditions converting Tertiary Propargyl Alcohols into 2,4-Substituted Quinolines

entry	R	[H]	H ⁺	Yield % ^a
1	<i>n</i> -butyl	Fe	HCl	95
2	"	TiCl ₃	HCl	< 40 ^b
3	"	Zn	AcOH	95
4	"	SnCl ₂	HCl	91
5	Phenyl	Fe	HCl	82

^a Isolated yield; ^b Yield determined by GC

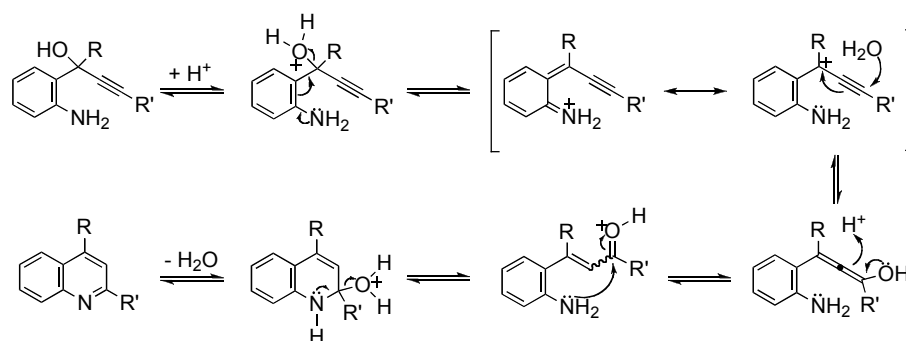
We propose this transformation occurs through a Meyer-Schuster rearrangement;^{189,190} the [1,3] propargylic shift of the hydroxyl group, followed by protonation of the resulting allenol, to produce an enone. Although this mechanism seems reasonable, repeated attempts to initiate this rearrangement on the secondary *o*-nitrophenyl propargyl alcohol **76** (Scheme 81) by both strongly acidic and basic conditions produced no enone.

Scheme 81



Based on this result, we believe this quinoline formation is only possible after reduction of the nitro group, due to the resonance-stabilization of the secondary alkynyl cation by the aniline (Scheme 82). This mechanism is also supported by the relative ease of quinoline formation from tertiary propargyl alcohols compared to the secondary propargyl alcohols (*vide infra*).

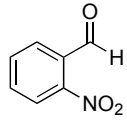

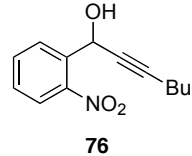
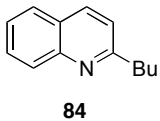
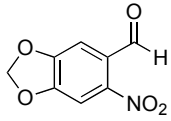
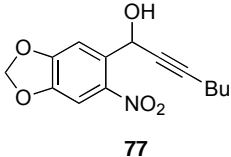
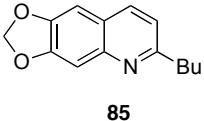
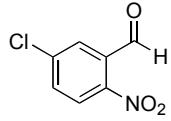
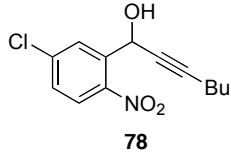
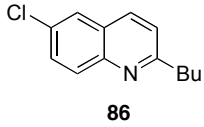
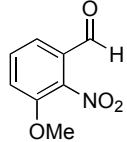
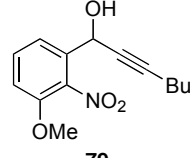
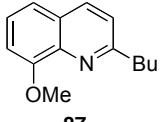
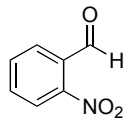
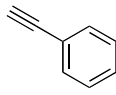
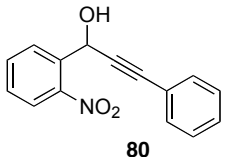
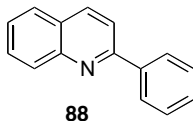
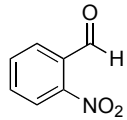
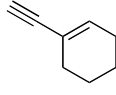
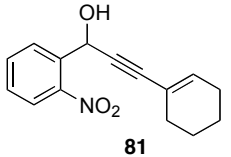
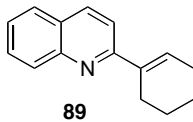
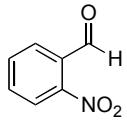
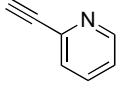
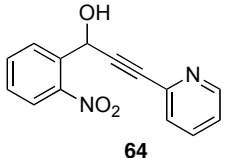
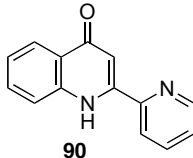
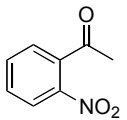
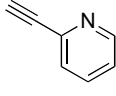
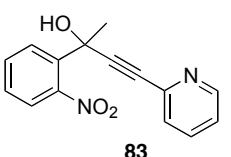
Scheme 82



In order to demonstrate the generality of this technique, a series of propargyl alcohols have been prepared, with subsequent reduction/cyclizations to quinolines (Table 2). Entries 1 and 5 depict the *n*-butyl and phenyl secondary propargyl alcohol analogues of those examined in Table 1. Both quinolines were formed in good yield, although not as high as their tertiary counterparts. Entries 2, 3 and 4 examine the electronic effects of A ring substituents on the cyclization, and the success of those transformations demonstrates that any such substituent effect is minimal. Entries 4 & 6 do show a lower yield than other examples, however that diminished yield appears to result from difficulty isolating the sensitive product rather than inherent limitations with the reaction in question. It is important to note the purification of these quinolines (**84-89**) was done by a combination of acid-base extractions and/or bulb-to-bulb distillations since these low molecular weight quinolines were generally unstable to either silica, alumina or florisil chromatography. In most cases the NMR spectra of crude product indicated the presence of the desired product in high purity; however, significant mass loss occurred during purification.

The pyridyl-substituted examples (entries 7 and 8) form the original impetus for this quinoline-forming reaction study, since the ultimate application of this quinoline heteroannulation with streptonigrin CD ring intermediate **2** requires formation of a 2-pyridylquinoline. Reductive cyclization of the pyridyl secondary propargyl alcohol **82** generated quinolone **90**, instead of the expected quinoline. Further examination of this result will be discussed in the later in this manuscript.

Table 2. Further Secondary and Tertiary Propargyl Alcohol Examples

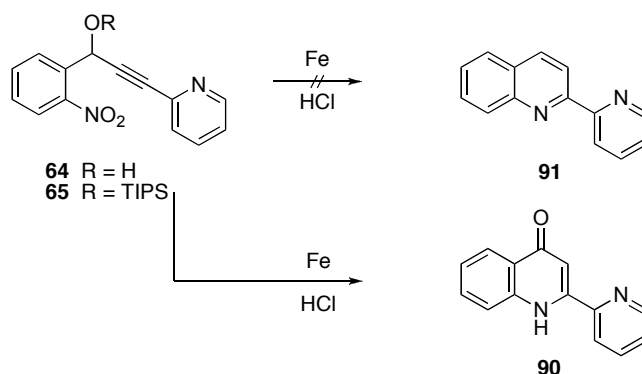
entry	Aldehyde/ Ketone	Acetylide	Propargyl Alcohol	Quinoline
1			 76	 84
		$\xrightarrow[n^{\circ}\text{C, THF}]{n\text{-BuLi}}$ 98%		$\xrightarrow[\text{AcOH}]{\text{Zn}}$ 79%
2		"	 77	 85
		$\xrightarrow[n^{\circ}\text{C, THF}]{n\text{-BuLi}}$ 59%		$\xrightarrow[\text{HCl}]{\text{Fe}}$ 82%
3		"	 78	 86
		$\xrightarrow[n^{\circ}\text{C, THF}]{n\text{-BuLi}}$ 76%		$\xrightarrow[\text{HCl}]{\text{Fe}}$ 68%
4		"	 79	 87
		$\xrightarrow[n^{\circ}\text{C, THF}]{n\text{-BuLi}}$ 96%		$\xrightarrow[\text{HCl}]{\text{Fe}}$ 44%
5			 80	 88
		$\xrightarrow[n^{\circ}\text{C, THF}]{n\text{-BuLi}}$ 97%		$\xrightarrow[\text{HCl}]{\text{Fe}}$ 64%
6			 81	 89
		$\xrightarrow[n^{\circ}\text{C, THF}]{n\text{-BuLi}}$ 97%		$\xrightarrow[\text{AcOH}]{\text{Zn}}$ 34%
7			 64	 90
		$\xrightarrow[n^{\circ}\text{C, THF}]{n\text{-BuLi}}$ 18%		$\xrightarrow[\text{HCl}]{\text{Fe}}$ 53%
8			 83	decomposition
		$\xrightarrow[n^{\circ}\text{C, THF}]{n\text{-BuLi}}$ 59%		$\xrightarrow[\text{HCl}]{\text{Fe}}$

In summary, the reduction-rearrangement of *o*-nitrophenyl propargyl alcohol derivatives provided 2-aryl-, 2-alkenyl and 2-alkylquinolines in good to excellent yield. The methodology is tolerant of both electron-donating and electron-withdrawing functionality on the A-ring and to substitution on the alkyne. The combination of mild Sonogashira coupling of aryl triflates to terminal propargyl alcohols, followed by direct reductive cyclization opens the door to the production of a variety of 2-arylquinolines with highly functionalized aryl groups, applicable to many quinoline-based natural product syntheses, including the synthesis of streptonigrin.

FINAL ABC RING MODEL SYSTEMS--QUINOLONE FORMATION

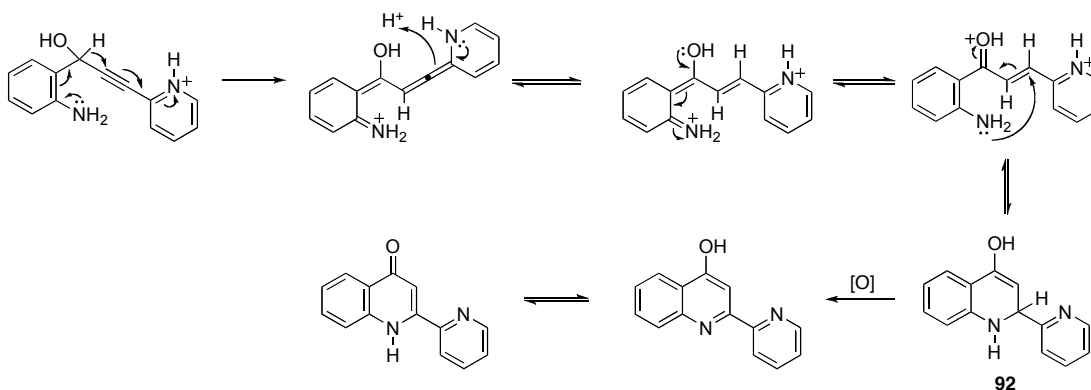
The application of our quinoline heteroannulation methodology to the synthesis of streptonigrin requires the reductive cyclization to proceed as previously described with a pyridine unit attached at the terminal end of the propargyl alcohol. Initial models of this system were described earlier, both in Scheme 77 and entry 7 in Table 2. In either case, the reductive cyclization produced no quinoline product **91**, instead the 4-quinolone **90** was produced (Scheme 83). In order to determine if our proposed route to streptonigrin is viable, two important issues would need to be resolved: (1) precisely how this anomalous model system product is formed instead of the quinolines formed by other model system propargyl alcohols, and (2) whether or not a more fully functionalized A ring precursor would follow the same undesired pathway.

Scheme 83



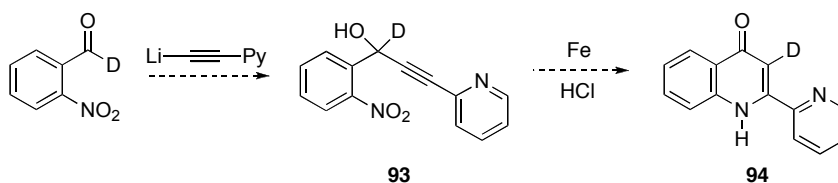
The generation of 4-quinolone **90** can be rationalized by two distinctive pathways: (1) cyclization by a distinctly different mechanism, propagated by the electronic nature of the pyridyl substituent, or (2) reductive cyclization as previously described, followed by post-cyclization oxidation of 2-pyridylquinoline to quinolone. One proposed mechanism for the former pathway (Scheme 84) involves a hydride shift, due to the electron-withdrawing nature of the pyridinium system at the terminal end of the alkyne. The resulting allene, once protonated, would produce an enone system capable of ring closure with the aniline A ring function, producing a dihydroquinoline **92**, which would be either air oxidized or oxidized by the iron salts already present in the reduction system.¹⁹¹

Scheme 84



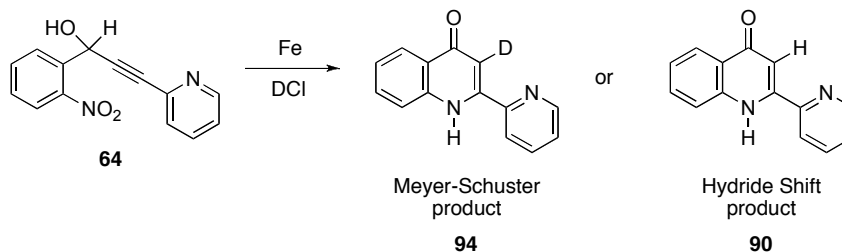
The occurrence of this mechanism could be tested by one of two deuterium labeling studies. Initially, we envisioned producing 1-deuteroaldehydes of our *o*-nitrobenzaldehyde, and following the previous sequence of propargyl alcohol production to generate deuterated propargyl alcohol **93**. If, in fact, a hydride (or deuteride) shift occurred, the resulting quinolone would have deuterium in the 3-position.

Scheme 85



However, a more expeditious route was taken where our currently available propargyl alcohol **64** was reductively cyclized in a deuterated solvent. These conditions would allow us to track the proposed hydride shift as the protium shifts, generating the same quinolone we previously isolated. If the Meyer-Schuster rearrangement occurred as previously described (Scheme 82), the protonation of the intermediate allenol would incorporate deuterium from the reaction solution, and the resulting quinolone would have deuterium at the 3-position (Scheme 86).

Scheme 86



Analysis of the crude NMR from this reaction showed the complete disappearance of the ^1H NMR singlet resonance at 6.62 ppm corresponding to the 3-position proton; the other ^1H NMR resonances of the 4-quinolone **90** were present. Isolation of this deuterated product was not done based on the potential for exchange of the deuterium with environmental protium. Purification of these pyridylquinoline/quinolone reactions is normally carried out with an acid/base extraction, the conditions of which could alter the protium/deuterium content of the product.

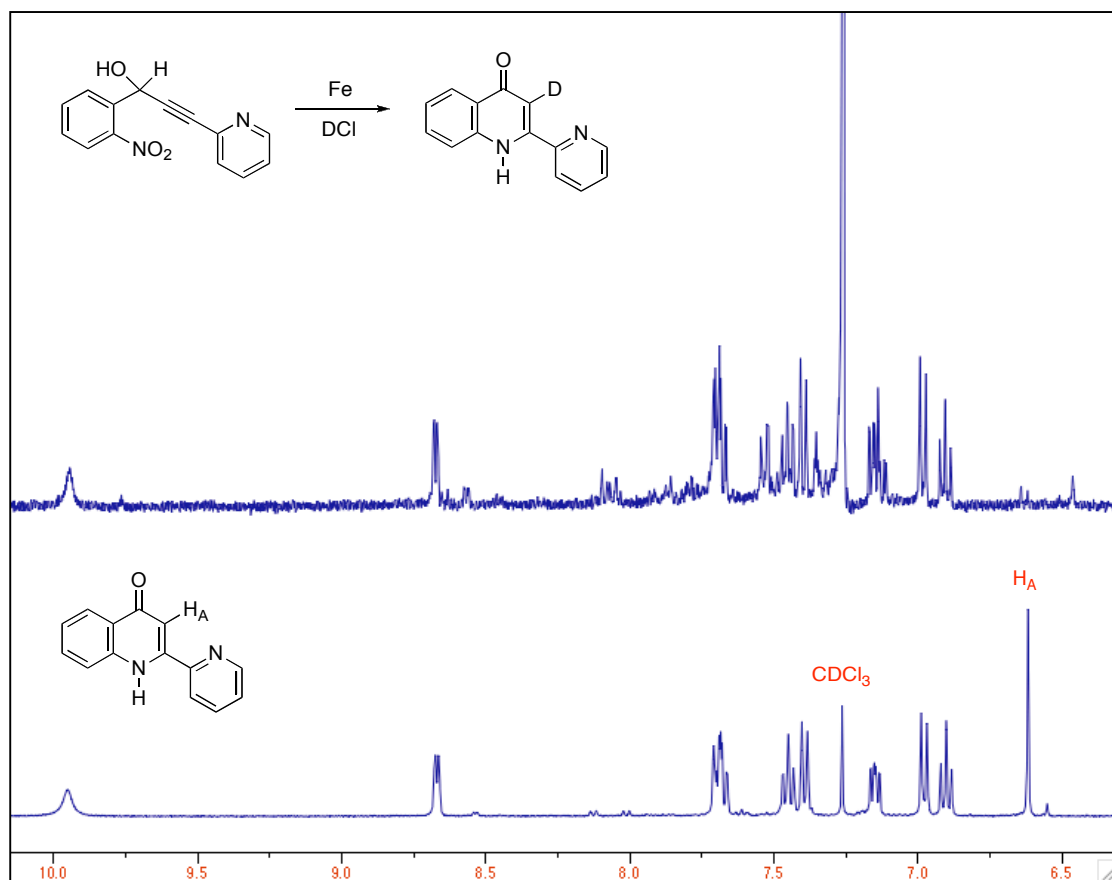
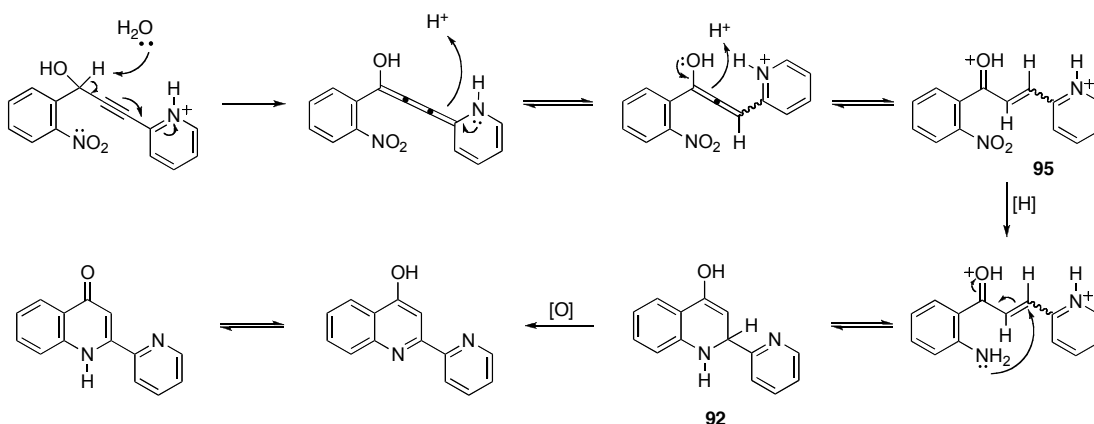


Figure 8. Reductive Cyclization in Fe/DCl (top); in Fe/HCl (bottom)

Another alternative rearrangement that would produce the same dihydroquinoline intermediate **92**, and therefore the same quinolone product, is depicted in Scheme 87. Deprotonation would produce a cumulene intermediate, which after protonation would produce regioisomeric enone **95** relative to our previous Meyer-Schuster intermediates. After reduction of the nitro group, cyclization could occur in a conjugate fashion, forming the same dihydroquinoline **92**. This dihydroquinoline is incapable of rearomatization via dehydration, and therefore persists until air oxidation to the hydroxyquinoline.

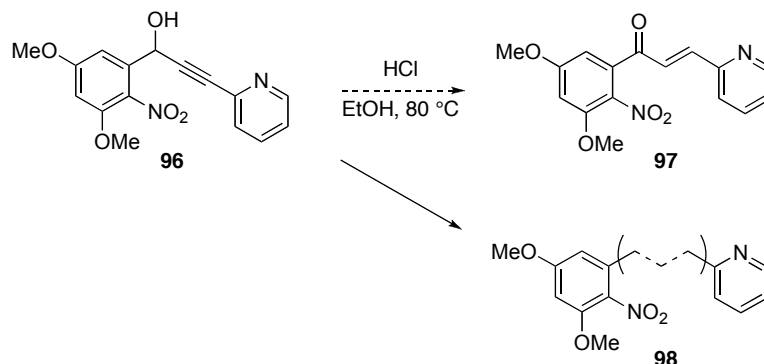
Scheme 87



This proposed mechanism would not be excluded by the aforementioned deuterium study. This pathway would also be independent of the reduction of the nitro group, and therefore could be tested solely under acid-catalyzed conditions. Propargyl alcohol **96** (synthesis to be discussed in the following A Ring chapter) was treated with HCl in ethanol at reflux for 7 hours, in which time the starting material

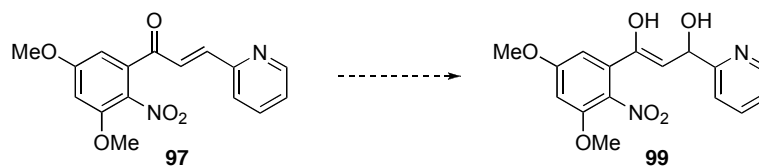
was completely consumed, and only one product was produced (Scheme 88). However, the exact structure of the resulting product was not definitively proven.

Scheme 88



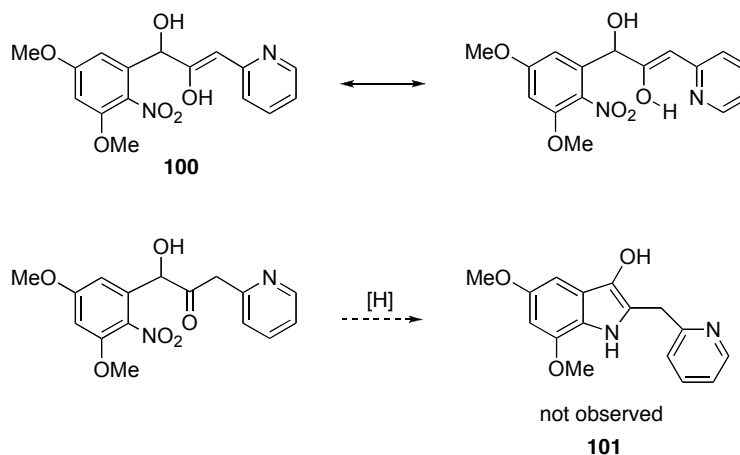
Both ^1H NMR and IR data confirm the structure of the pyridine and A rings are intact, including the aromatic resonances for the four pyridyl protons and the two A ring protons, as well as the methoxy groups. The IR data confirms the existence of the nitro group, and shows a weak, broad stretch across the $3500\text{--}2500\text{ cm}^{-1}$ range which could be an O-H stretch. The IR does not show any carbonyl stretch. The ^{13}C NMR spectrum also shows no carbonyl resonance, therefore excluding the proposed enone **97**. The remaining resonances on the ^1H NMR spectrum appear at 5.57 and 7.45 ppm, with corresponding ^{13}C NMR resonances at 72.9 and 125.4 ppm, respectively. These two resonances are also show weak coupling ($J = 1\text{ Hz}$). One potential structure of **98** that would match these data would be the hydrated enone **99**, however there is no clear reason to expect to isolate the enol tautomer.

Scheme 89



Another possible structure for this product would be enol **100**, which is the result of acid-catalyzed hydration of the triple bond (Scheme 90). This structure also matches the characterization data, and would be stable in the enol tautomeric form based on six-membered ring hydrogen bonding with the pyridine. However, this enol would be expected to cyclize, after reduction of the nitro group, to form hydroxyindole **101**, which has not been observed.

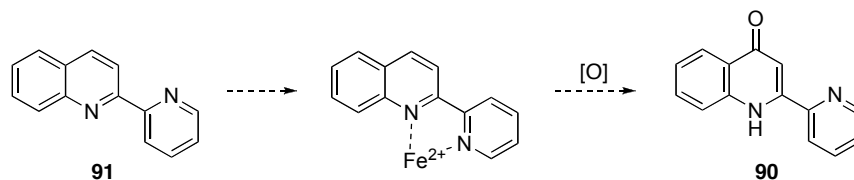
Scheme 90



A third potential avenue for quinolone formation would involve quinoline cyclization through the Meyer-Schuster rearrangement and reductive cyclization,

followed by oxidation of the quinoline to quinolone. This could occur through Fenton-type chemistry, with the resulting iron salts. This was not observed in any non-pyridyl systems, but would be potentiated by the strong phenanthroline-like chelation of iron by both the quinoline and pyridine nitrogens.

Scheme 91



An oxidation of this nature could only be proven through production of 2-pyridylquinoline **91** by other means, and then subjected to similar reductive cyclization conditions. This avenue was not tested. However, a recent study utilized Fe/HCl as the reducing agent in the Friedlander synthesis of 2-pyridylquinoline **91**, with excellent yield and no reported post-cyclization oxidation.⁷⁷

Despite the lack of definitive identification of **98**, the fact that propargyl alcohol **96** was capable of a non-Meyer-Schuster rearrangement under acidic conditions supports the contention that an alternative rearrangement is producing the observed quinolone. Future efforts to apply this reductive cyclization to the synthesis of 2-pyridylquinoline must focus on finding conditions to eliminate this alternative rearrangement.

Application to the Total Synthesis of Streptonigrin--A Ring Synthesis

In order to exploit the aforementioned quinoline heteroannulation methodology to the synthesis of streptonigrin, an A ring intermediate aldehyde must be generated with the proper functionality to ultimately arrive at streptonigrin's methoxy-aminoquinone moiety. The two aldehydes targeted in this work are 3,5-dimethoxy-2-nitrobenzaldehyde (**102**), and 3,5-dimethoxy-2,4-dinitrobenzaldehyde (**103**) (Figure 9). Both aldehydes have a methoxy group in the correct position to direct oxidation to the *p*-quinone, as well as the methoxy group in the final 6-position of streptonigrin. Both aldehydes have the nitro group *ortho* to the aldehyde required for cyclization, however dinitroaldehyde **103** also has a nitro group positioned to be reduced concurrently with cyclization to generate streptonigrin's 7-amino function. This facet makes dinitroaldehyde **103** a more intriguing target, and the subject of the bulk of this investigation.

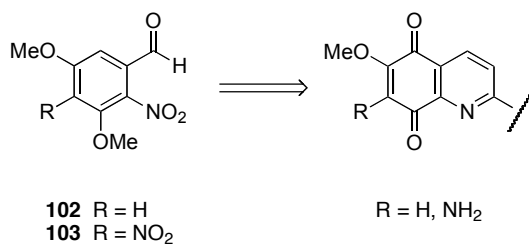
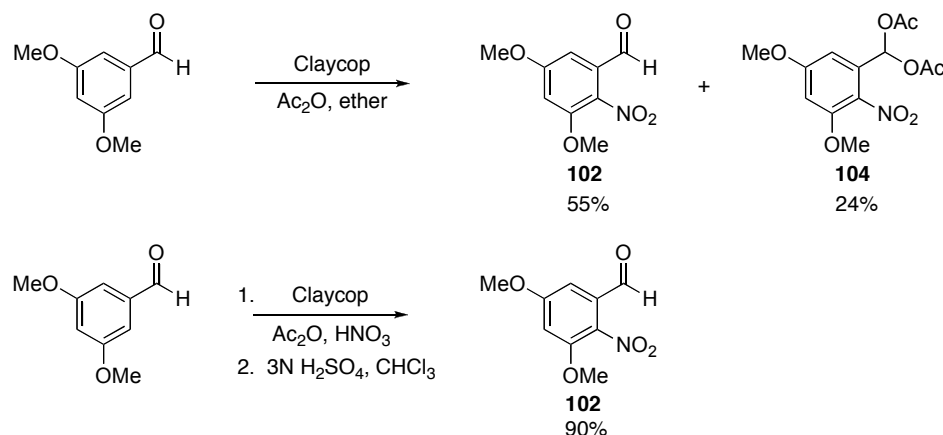


Figure 9. Target Aldehydes for Streptonigrin AB-Ring System Synthesis

Mononitroaldehyde **102** is a known compound, that was previously generated via direct nitric acid nitration of 3,5-dimethoxybenzaldehyde in 64% yield.¹⁹² In our

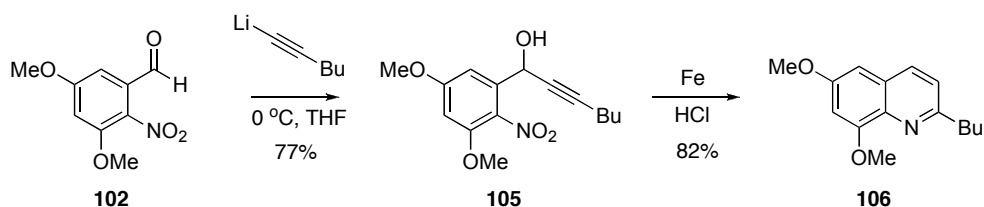
hands, the direct mononitration of the same commercially available 3,5-dimethoxybenzaldehyde was best accomplished via a mild copper nitrate/Montmorillonite clay “claycop” procedure developed by Laszlo.¹⁹³ This reaction was initially accomplished without the addition of nitric acid, and was complicated by a large amount of the gem-diacetate byproduct **104**. The formation of this byproduct was minimized by the addition of small amounts of nitric acid, and any remaining gem-diacetate was cleaved in an acidic workup step, leading to an improved 90% yield of the desired mononitrated aldehyde **102** (Scheme 92).

Scheme 92



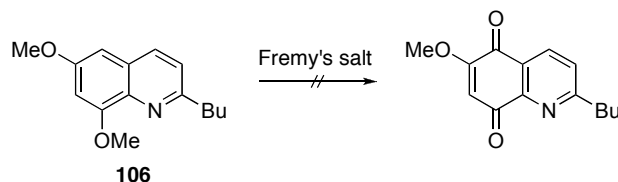
Direct access to this targeted aldehyde in a high-yielding single step process allowed the further modeling of the quinoline methodology to form streptonigrin-like AB ring systems. Addition of the lithium acetylide of 1-hexyne, as previously reported, formed the propargyl alcohol **105** in high yield, and the Fe/HCl reductive cyclization conditions formed 2-butyl-6,8-dimethoxyquinoline **106** in 82% yield (Scheme 93).

Scheme 93



Dimethoxyquinoline **106** was also subjected to initial screening of oxidation conditions to prepare the quinoline-5,8-dione moiety of streptonigrin. However, Fremy's salt oxidation was not sufficient to accomplish this transformation, leaving the starting quinoline unaffected. Further studies with more robust oxidizing agents must be done in the future to confirm the potential of this oxidation.

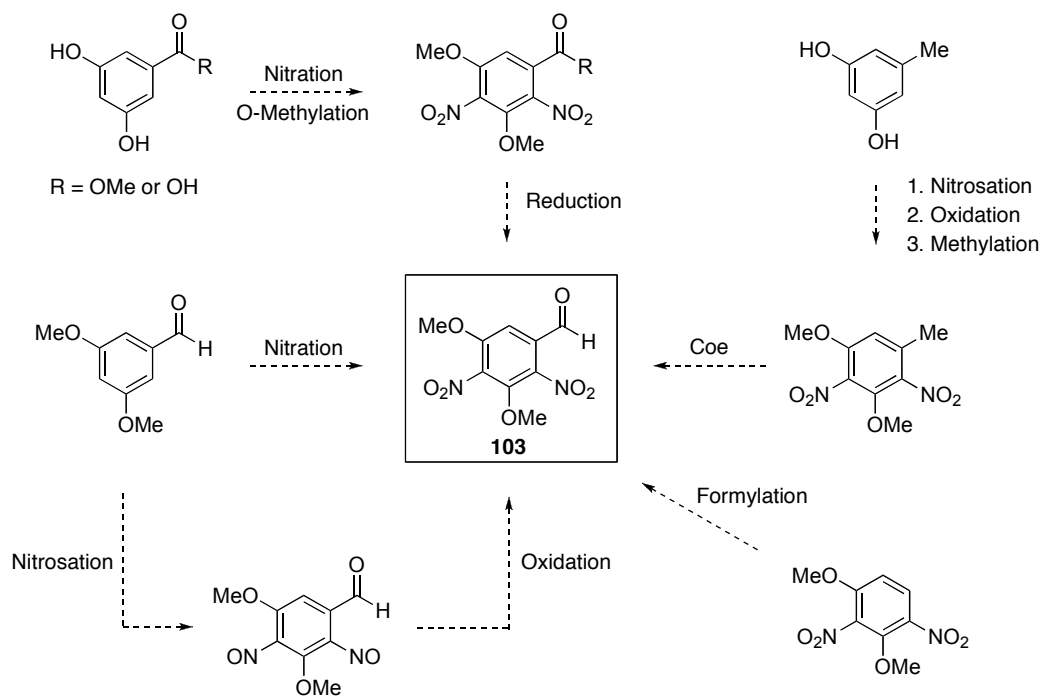
Scheme 94



The application of mononitroaldehyde **102** synthesis to streptonigrin, although expeditious, would ultimately leave the addition of the A ring 7-amino function to be accomplished at the end. This addition has been well-precedented in the synthesis of many of the streptonigrinoid compounds, by the three-step sequence developed by Cheng¹⁵⁹ (Scheme 56). However, we sought to eliminate those post-cyclization manipulations by developing a synthesis of dinitrobenzaldehyde **103**, and applying that A ring precursor to the synthesis of streptonigrin.

Our efforts to synthesize dinitroaldehyde **103** took several paths, developed to control the regioselectivity of the dinitration, while maintaining the ability to introduce the aldehyde functionality (Scheme 95).

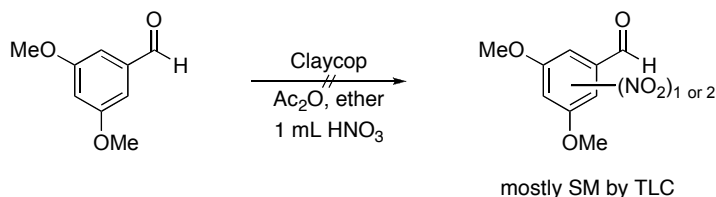
Scheme 95



Our initial success with claycop nitration led to the investigation of claycop's potential to dinitrate orcinol derivatives. In their report, Laszlo *et al.* described the addition of fuming nitric acid to claycop reactions to initiate dinitration. However, none of the substrates used in that dinitration work contained oxidizable functional groups like an aldehyde. In our hands, the addition of small amounts of concentrated nitric acid were necessary to limit the amount of gem-diacetate protection of our aldehyde in the acetic anhydride reaction mixture. However, large amounts of nitric

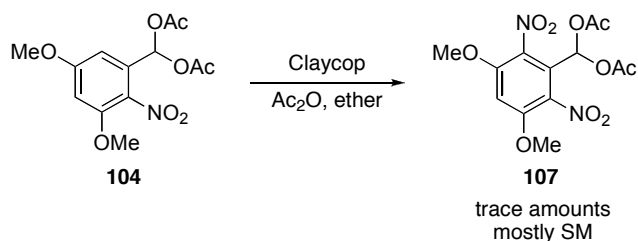
acid dictated by Laszlo's report did not achieve dinitration (Scheme 96). In fact, when additional nitric acid was added, nitration was inhibited, rather than activated.

Scheme 96



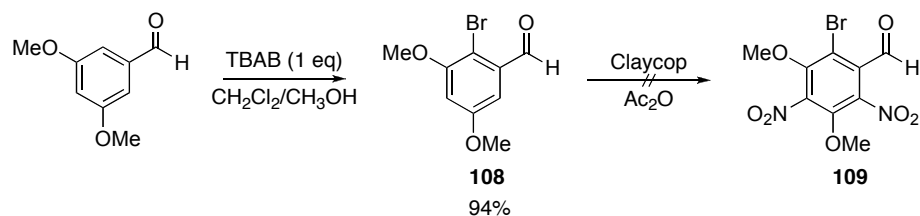
The gem-diacetate byproduct **104** of our initial claycop mononitrations was also resubjected to claycop nitration conditions. We anticipated that the steric bulk of the acetates might direct any second nitration to the *para* position, leading to the desired dinitrated regiochemistry. However, only trace amounts of a dinitrated product **107** were isolated, and the symmetry of that products NMR spectra indicated that the second nitro group was also added in the *ortho* position. Accordingly, this avenue was not pursued further.

Scheme 97



To control the regioselectivity of the second nitration, bromine was used as a blocking group. Bromination of dimethoxybenzaldehyde with tetrabutylammonium tribromide¹⁹⁴ yielded the known bromoaldehyde **108** in excellent yield. Dinitration of that bromoaldehyde under claycop conditions resulted in only low yields of mononitrated product, and most importantly, no dinitrated aldehyde **109**.

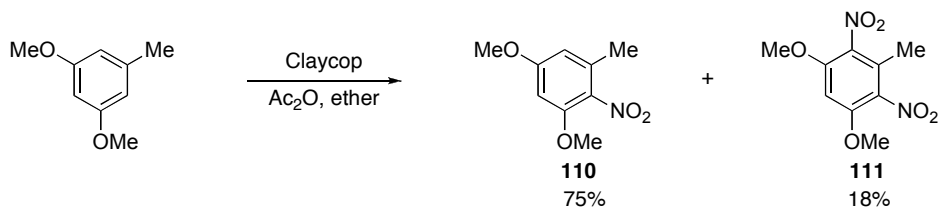
Scheme 98



The only other direct dinitration reaction condition attempted on this aldehyde was using nitronium tetrafluoroborate. This nitrating agent developed by Olah¹⁹⁵ has been used on many occasions, reportedly due to its robust nitrating capability without the inherent oxidizing nature of mixed acid nitrations. However, in our hands, nitration of dimethoxybenzaldehyde with 2.5 eq of nitronium tetrafluoroborate provided low yields of mononitrated product **102**, and significant decomposition.

Since direct dinitration of a benzaldehyde intermediate could not be achieved, the next avenue investigated was dinitration of toluene compounds, leaving the subsequent benzylic oxidation of that toluene methyl group for a later step. Claycop nitration of 3,5-dimethoxytoluene resulted in a poor yield of dinitrated product **111**, with the same undesired regiochemistry as previously discussed.

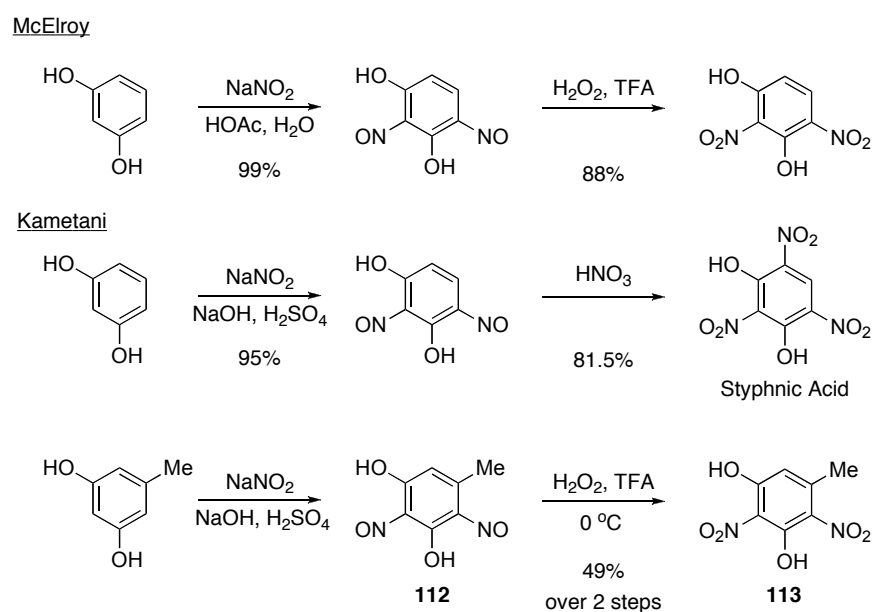
Scheme 99



The possibility of the two methoxy groups sterically controlling this nitration led us to examine the use of orcinol (3,5-dihydroxytoluene) as a starting material. Since claycop nitrations require the use of acetic anhydride, which acylated the phenols, complicating any nitration of orcinol, we examined a nitrosation/nitration sequence.

A two-step nitrosation/oxidation of resorcinol was utilized by McElroy, in one of his A ring precursors (Scheme 100). These conditions were a modification of those originally reported in 1967 by Kametani in his synthesis of the explosive styphnic acid. McElroy replaced the nitric acid oxidation of the nitroso groups with trifluoroacetic peracid oxidation to avoid the concomitant trinitration (Scheme 100). Application of this nitrosation/oxidation sequence to orcinol was also effective in producing the desired dinitrated toluene derivative **113**.

Scheme 100



In a fashion similar to McElroy's observations of dinitrosoresorcinol, the intermediate dinitroso compound **112** was relatively stable, however attempts to recrystallize this brown powder led to decomposition. Therefore crude **112** was carried forward into the oxidation conditions, and the reported 49% yield for this sequence was over both dinitrosation and oxidation steps. Further optimization of

this oxidation reaction could significantly improve the yield. It was observed that excess hydrogen peroxide significantly diminished the yield of **113**. Careful titration of fresh hydrogen peroxide (nominally 30% as commercially available) before its use could prevent any further degradation of the product. This type of optimization was postponed pending the validation of this route to our desired dinitroaldehyde.

The product of this nitrosation/oxidation sequence appeared to favor the desired regiochemistry, and X-ray analysis of **113** confirmed that regioselectivity (X-ray data in Appendix). This observed regiochemistry seemed surprising at first, in light of our aforementioned direct nitration results; but after careful examination of the literature,^{196,197} the result was reasonably predictable (Figure 10). After initial nitrosation at the same position *ortho* to the methyl group as we observed in mononitrations, the resulting nitrosophenol has a stable tautomeric form as a *p*-quinone-oxime **114**. This quinone-oxime would be preferentially nitrosated at the enolic position, leading to the desired 2,4-dinitrosoorcinol **112**, in its diketo tautomeric form. The infrared spectrum of this compound showed absorbances at 1695 and 1646 cm^{-1} , corresponding to that quinone-oxime tautomer (Figure 11).

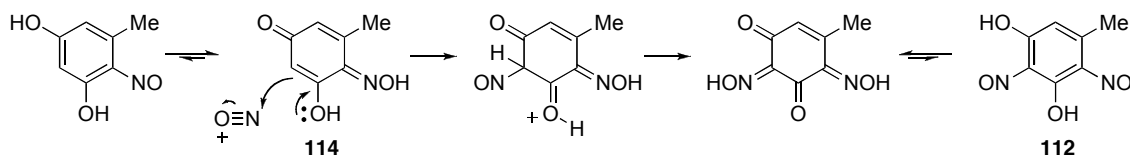


Figure 10. Regioselectivity in Dinitrosation of Orcinol

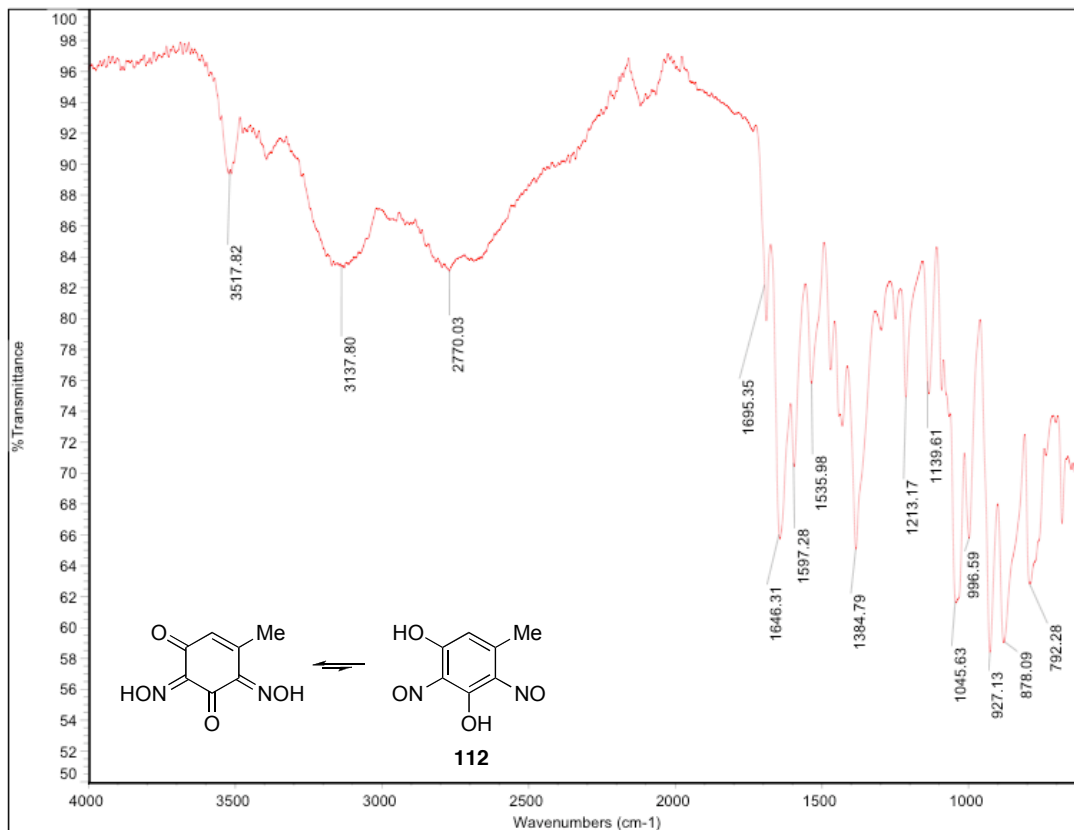
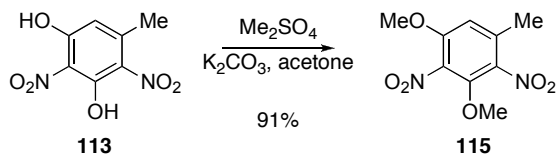


Figure 11. Infrared Spectrum of Dinitrosoorcinol

Facile *O*-alkylation of dinitrotoluene **113** using standard dimethyl sulfate conditions led to 3,5-dimethoxy-2,4-dinitrotoluene **115** in excellent yield. Compound **115** required only benzylic oxidation of the methyl group to an aldehyde to successfully synthesize our desired A ring intermediate. Unfortunately, this oxidation proved much more difficult than we anticipated.

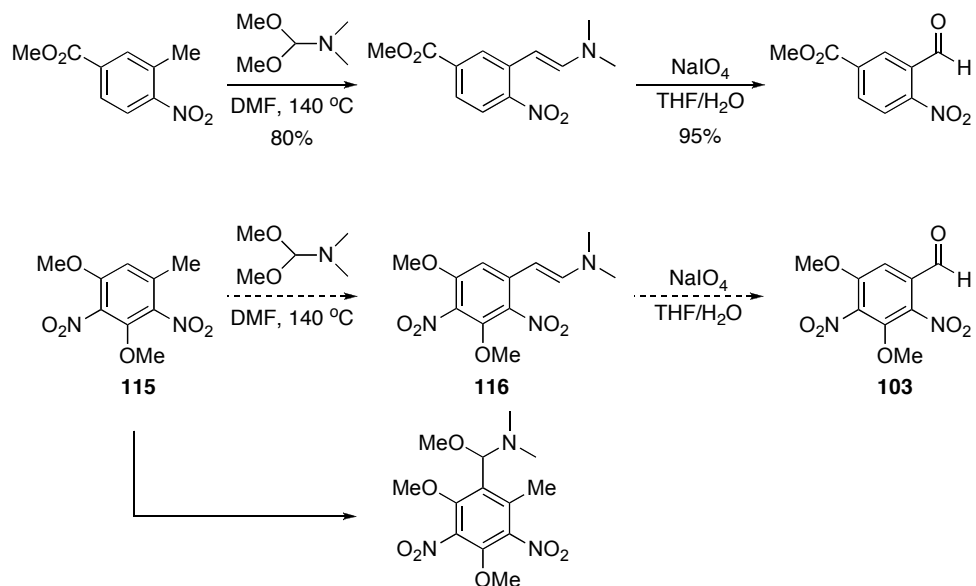
Scheme 101



Several oxidation schemes were envisioned to arrive at the desired aldehyde. Our first attempts were guided by a recent seminar presented by Dr. Jotham Coe from Pfizer Inc. Dr. Coe directed us to his recently published method of converting nitrotoluene derivatives to aldehydes, achieved by a two-step process of forming enamines with *N,N*-dimethylformamide dimethyl acetal and oxidative cleavage of that enamine to the desired aldehyde with sodium periodate. This transformation was demonstrated on a variety of nitroarenes (Scheme 102), however none with the methoxy groups our substrate would require (Scheme 102).

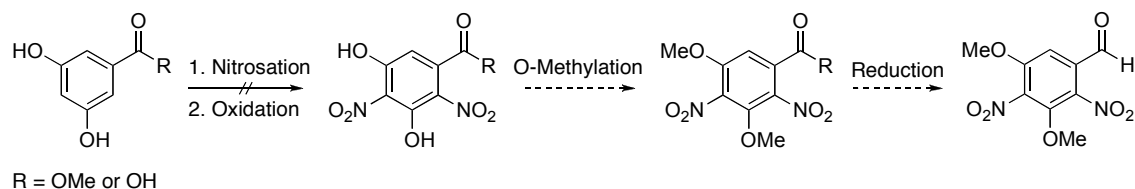
Repeated attempts to produce enamine **116** via the Coe methodology on these systems however failed. The conditions were modified to include amine bases as has been done by others,^{198,199} including pyrrolidine and Hunig's base, however no enamine was detected. In each case, the starting toluene **115** was consumed in the process, but the product always contained the toluene methyl group unfunctionalized. The likely product of this reaction was electrophilic aromatic substitution, however since this is clearly not the desired transformation, little effort was directed at characterizing this byproduct. Further efforts at the direct benzylic oxidation of **115** were attempted with known oxidation systems, including selenium dioxide and potassium permanganate. In no case did those oxidations provide the desired aldehyde.

Scheme 102



The final potential pathway to the dinitrated A ring precursor **103** that we explored involved the dinitrosation/oxidation on orcinol-like substrates that already included an oxidated toluene methyl carbon: 3,5-dihydroxybenzoic acid and methyl 3,5-dihydroxybenzoate. If either of these compounds regioselectively dinitrosated as orcinol did, the resulting benzoate or benzoic acid functionality could be selectively reduced. This would need to be done in the presence of reducible nitro groups, however, the low-temperature reduction of esters to aldehydes by DIBAL is a possible solution. Unfortunately, nitrosation of neither carboxylic acid or ester proved successful.

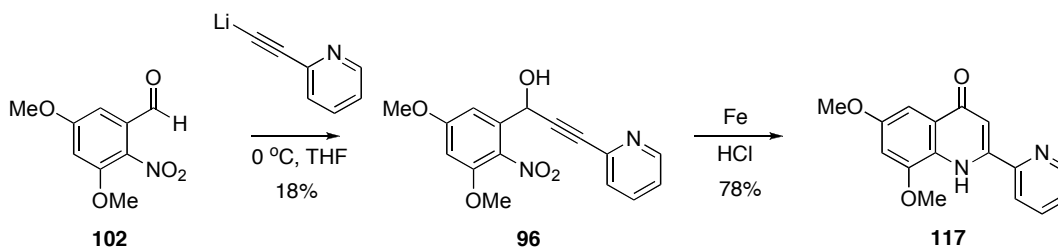
Scheme 103



Since none of our examined routes generated the desired dinitrobenzaldehyde **102**, the remaining efforts in this work were focused on the elaboration of the mononitrated A ring precursor benzaldehyde **102** into 2-pyridylquinolines.

Mononitrobenzaldehyde **102** was treated with the lithium acetylide of 2-ethynylpyridine to form propargyl alcohol **96**, in poor, unoptimized 18% yield. This propargyl alcohol was then subjected to reductive cyclization conditions, producing the expected, yet undesired, quinolone **117** in good yield.

Scheme 104



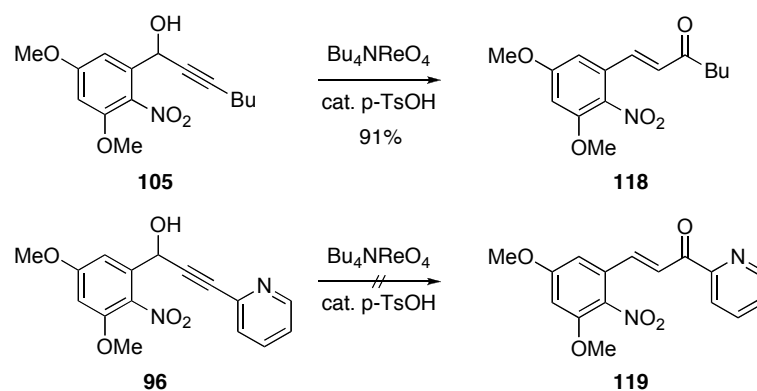
Conclusion

The desired synthesis of the AB-quinolinequinone ring system of the antitumor antibiotic streptonigrin has led to the development of a new methodology for synthesizing quinolines. The utilization of *o*-nitrophenyl propargyl alcohols, produced either through direct lithium acetylide addition of available alkynes, or Sonogashira coupling to terminal propargyl alcohols, has led to the facile synthesis of 2-aryl-, 2-alkenyl and 2-alkylquinolines via reductive cyclization under mildly acid conditions. Several examples of this methodology have been produced, with a variety of electron-donating and electron-withdrawing substituents on the carbocyclic ring of quinoline, proving the versatility of the reductive cyclization.

The application of this methodology to the 2-pyridylquinoline system required to synthesize streptonigrin has identified an anomalous cyclization, leading to quinolone formation, instead of the desired quinoline. This cyclization has been studied mechanistically, and several possible mechanisms have been proposed and evaluated. The evidence presented favors the rearrangement of the pyridyl-substituted propargyl alcohol to an enone derivative that is not capable of aromatizing to quinoline. Oxidative rearomatization leads to the observed quinolone. Future efforts to apply this methodology to the synthesis of 2-pyridylquinoline must address this anomalous rearrangement. One potential avenue to circumvent that rearrangement is the Meyer-Schuster rearrangement catalyzed by a transition metal instead of acid. Initial screening of rhenium-catalyzed Meyer-Schuster rearrangement¹³⁴ on dimethoxy propargyl alcohol **105** produced enone **118** in excellent yield. Although one attempt to apply this rhenium catalysis to the pyridyl propargyl alcohol **96** did not produce

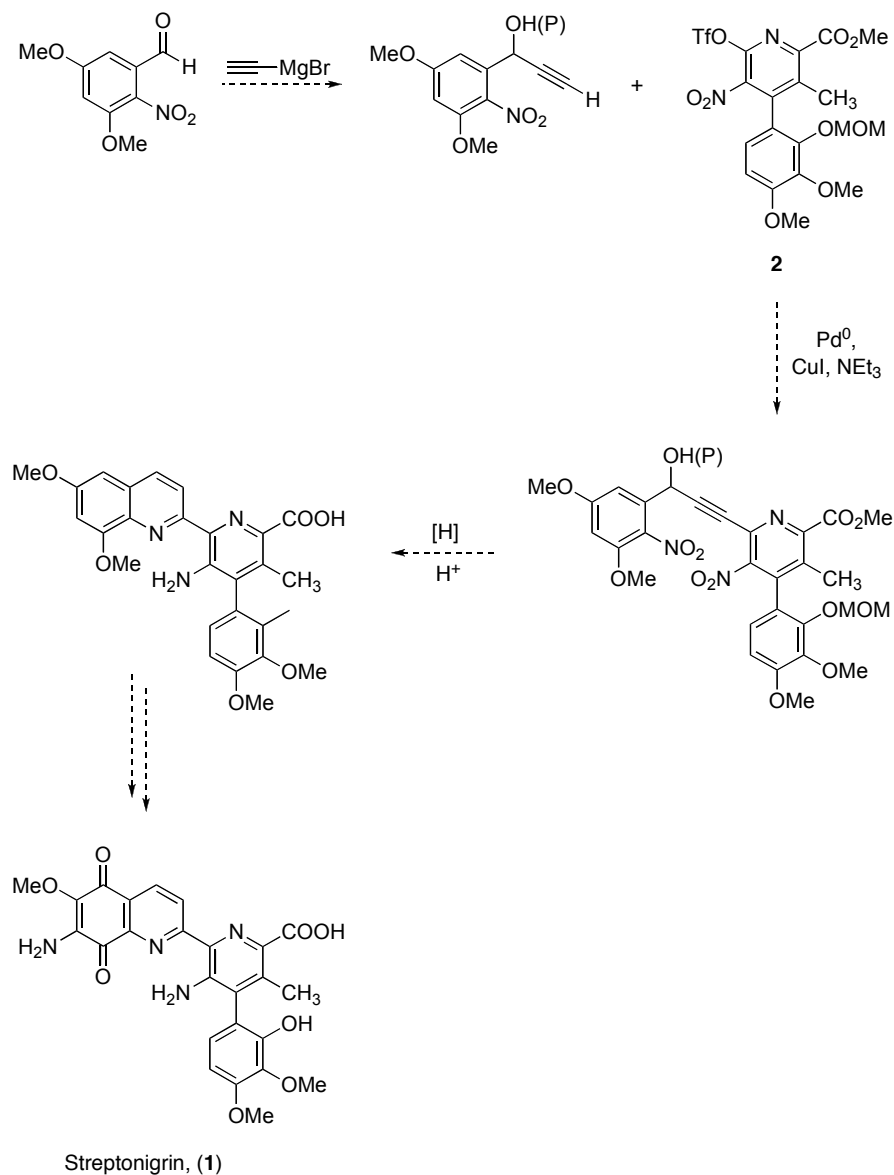
enone **119**, the basic pyridine may have scavenged the catalytic amount of *p*-toluenesulfonic acid required. Further examination of this and other transition-metal catalyzed Meyer-Schuster rearrangements may open the door for a two-step reductive cyclization of **96** to the desired quinoline, thus avoiding the quinolone observed in this study.

Scheme 105



Lastly, extensive efforts toward the synthesis of the proposed A-ring precursor, dimethoxydinitrobenzaldehyde were described. Although this synthesis was not achieved, the benefit of its use in dramatically shortening the total synthesis of streptonigrin dictate further study. The use of mononitrobenzaldehyde **102**, although synthesized in this work in a high-yielding, one-step process, leaves the final 7-amino functionality of streptonigrin to be developed at the end of the synthesis.

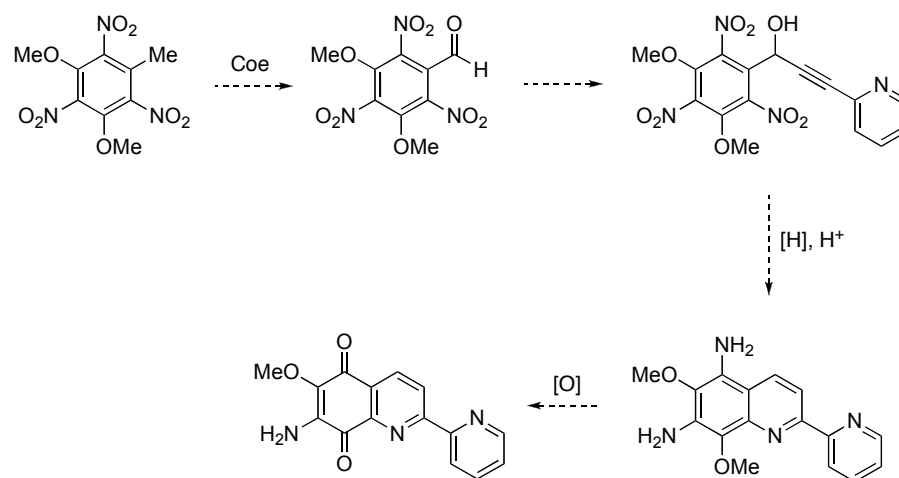
Scheme 106



Another potential avenue not explored in this work includes the generation of trinitroorcinol, as described by Rao.¹⁶⁰ Although this compound has the potential to be an explosive, the third nitro group would further activate it toward the enamine formation required for the Coe methodology to produce the aldehyde. The third nitro group would also serve to block the final aromatic position, eliminating the

competing electrophilic aromatic substitution. Lastly, once reduced, the third nitro group (now amino) would facilitate oxidation to the quinoline-quinone. These features make this trinitroorcinol an intriguing, albeit potentially dangerous, A-ring precursor.

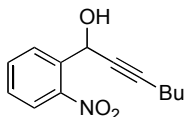
Scheme 107



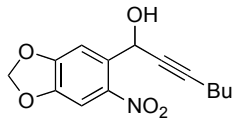
Overall, the DeShong group's progress toward the total synthesis of streptonigrin has been greatly advanced by this work. With additional studies on the reductive cyclization of pyridyl-substituted propargyl alcohols, 2-pyridylquinolines can be produced, and thus the application of this quinoline heteroannulation should provide streptonigrin in short order.

Experimental Procedures

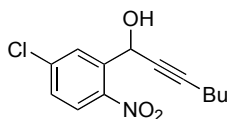
1-(2-Nitrophenyl)-hept-2-yn-1-ol **76**



A solution of 3.66 mL (31.7 mmol) of 1-hexyne in 25 mL anhydrous THF was cooled to 0 °C, and 13.0 mL (26.0 mmol) of 2.0M *n*-butyl lithium was added dropwise. The resulting solution was stirred for 30 min at 0 °C, and then 2.40 g (15.9 mmol) of *o*-nitrobenzaldehyde dissolved in 5 mL anhydrous THF was added dropwise via cannula. The mixture was stirred at 0 °C for a subsequent 60 min, then quenched with water. The THF was removed *in vacuo*, and the residue was dissolved in diethyl ether, washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Purification by filtration through a short column of silica gel with chloroform gave 3.64 g (98%) of **76** as a pale brown oil. IR (thin film, NaCl) 3405 (br s), 3105 (w), 3074 (w), 3039 (w), 2959 (s), 2934 (s), 2872 (s), 2277 (w), 2228 (w), 1609 (m), 1579 (m), 1529 (s), 1352 (s), 1012 (s) cm⁻¹; ¹H NMR (CDCl₃) δ 0.91, (t, *J* = 7 Hz, 3H), 1.40 (m, 2H), 1.51 (m, 2H), 2.25 (dt, *J* = 2, 7 Hz, 2H), 3.05 (d, *J* = 6 Hz, 1H), 5.97 (d, *J* = 6 Hz, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.67 (t, *J* = 8 Hz, 1H), 7.94 (d, *J* = 8 Hz, 2H); ¹³C NMR (CDCl₃) δ 13.5, 18.4, 21.9, 30.4, 61.5, 77.8, 88.2, 124.9, 129.1, 129.4, 133.6, 136.0, 148.2; HRMS (FAB⁺, M+Li⁺) *m/z* for C₁₃H₁₅NO₃Li⁺ calcd 240.1212, found 240.1214.

1-(6-Nitrobenzo[d][1,3]dioxol-5-yl)-hept-2-yn-1-ol 77

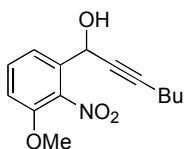
Produced by the same procedure as **76**, using commercially available 6-nitropiperonal. Column chromatography (chloroform, $R_f = 0.26$) yielded **77** as a pale orange oil (72%). IR (thin film, NaCl) 3526 (br s), 3411 (br s), 3121 (w), 3068 (w), 2958 (m), 2933 (m), 2872 (m), 2285 (w), 2228 (w), 1617 (m), 1524 (s), 1505 (s), 1484 (s), 1333 (s), 1262 (s), 1035 (s), 930 (m), 883 (m); ^1H NMR (CDCl_3) δ 0.90 (t, $J = 7$ Hz, 3H), 1.39 (m, 2H), 1.50 (m, 2H), 2.24 (t, $J = 7$ Hz, 2H), 3.16 (br s, 1H), 5.95 (s, 1H), 6.13 (s, 2H), 7.41 (s, 1H), 7.47 (s, 1H); ^{13}C NMR (CDCl_3) δ 13.5, 18.4, 21.9, 30.4, 61.3, 77.9, 87.9, 103.1, 105.7, 108.4, 133.6, 142.0, 147.6, 152.1; HRMS (FAB $^+$, $\text{M}+\text{Li}^+$) m/z for $\text{C}_{14}\text{H}_{15}\text{NO}_5\text{Li}^+$ calcd 284.1110, found 284.1116.

1-(5-Chloro-2-nitrophenyl)-hept-2-yn-1-ol 78

Produced by the same procedure as **76**, using commercially available 5-chloro-2-nitrobenzaldehyde. Recrystallization of the crude solid from hexanes yielded **78** as a pale yellow solid, mp 43.5-44.5 °C (59%). IR (thin film, NaCl) 3531 (br s), 3417 (br s), 3103 (w), 2959 (m), 2934 (m), 2873 (m), 2279 (w), 2230 (m), 1603 (s), 1571 (s), 1527 (s), 1466 (m), 1344 (s), 1078 (s), 843 (s); ^1H NMR (CDCl_3) δ 0.90 (t, $J = 8$ Hz, 3H), 1.39 (m, 2H), 1.49 (m, 2H), 2.23 (t, $J = 7$ Hz, 2H), 3.03 (br s, 1H), 6.01 (s, 1H), 7.44 (d, $J = 8$ Hz, 1H), 7.94 (m, 2H); ^{13}C NMR (CDCl_3) δ 13.5, 18.4, 21.9, 30.3, 60.9,

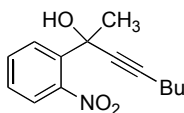
88.6, 126.4, 129.0, 129.3, 138.1, 140.1, 146.1; Anal. calcd for $C_{13}H_{14}NO_3Cl$: C, 58.32; H, 5.27; N, 5.23, found: C, 58.43; H, 5.27; N, 5.17.

1-(3-Methoxy-2-nitrophenyl)-hept-2-yn-1-ol **79**



Produced by the same procedure as **76**, using commercially available 3-methoxy-2-nitrobenzaldehyde. Filtration of the crude reaction mixture through a short column of silica with chloroform yielded **79** as a pale orange oil (96%). IR (thin film, NaCl) 3529 (br s), 3406 (br s), 3094 (w), 3021 (w), 2958 (m), 2935 (m), 2873 (m), 2285 (w), 2233 (w), 1607 (w), 1585 (m), 1535 (s), 1478 (m), 1370 (m), 1282 (s), 1024 (m), 853 (m), 761 (m); 1H NMR ($CDCl_3$) δ 0.90 (t, $J = 8$ Hz, 3H), 1.39 (m, 2H), 1.50 (m, 2H), 2.24 (m, 2H), 2.71 (br s, 1H), 3.90 (s, 3H), 5.56 (s, 1H), 7.02 (d, $J = 8$ Hz, 1H), 7.34 (d, $J = 8$ Hz, 1H), 7.45 (t, $J = 8$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 18.5, 22.1, 30.5, 56.7, 61.3, 77.5, 88.8, 112.9, 119.9, 131.7, 134.6, 140.0, 151.3; HRMS (FAB $^+$, $M+Li^+$) m/z for $C_{14}H_{17}NO_4Li^+$ calcd 270.1318, found 270.1326.

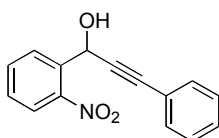
2-(2-Nitrophenyl)-oct-3-yn-2-ol **72**



Produced by the same procedure as **76**, using commercially available 2-nitroacetophenone. Radial chromatography (4:1 hexanes/ethyl acetate, $R_f = 0.40$) yielded **72** as a pale orange oil (59%). IR (thin film, NaCl) 3527 (br s), 3076 (w),

2959 (m), 2934 (m), 2872 (m), 2244 (w), 1532 (s), 1364 (s), 1219 (m), 1108 (m), 1083 (m), 917 (m), 855 (m), 779 (m), 750 (m); ^1H NMR (CDCl_3) δ 0.91 (t, J = 8 Hz, 2H), 1.38 (m, 2H), 1.47 (m, 2H), 1.95 (s, 3H), 2.20 (t, J = 8 Hz, 2H), 3.34 (s, 1H), 7.41 (dt, J = 1, 8 Hz, 1H), 7.54 (m, 2H), 7.80 (dd, J = 1, 8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 13.5, 18.3, 22.0, 30.3, 31.3, 68.0, 81.7, 86.0, 124.4, 127.4, 128.6, 131.8, 138.3, 149.8; HRMS (FAB $^+$, $\text{M}+\text{Li}^+$) m/z calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3\text{Li}^+$ calcd 254.1368, found 254.1376.

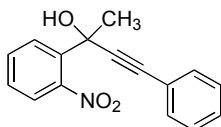
1-(2-Nitrophenyl)-3-phenyl-prop-2-yn-1-ol **80**



A solution of 2.60 mL (23.7 mmol) of phenylacetylene in 30 mL anhydrous THF was cooled to 0 °C, and 9.0 mL (18.0 mmol) of 2.0M *n*-butyl lithium was added dropwise. The resulting solution was stirred for 30 min at 0 °C, and then 2.45 g (16.2 mmol) of *o*-nitrobenzaldehyde dissolved in 5 mL anhydrous THF was added dropwise via cannula. The mixture was stirred at 0 °C for a subsequent 60 min, then quenched with water. The THF was removed *in vacuo*, and the residue was dissolved in diethyl ether, washed with water and brine, dried over MgSO_4 and concentrated *in vacuo*. Column chromatography (chloroform, R_f = 0.41) yielded 4.00 g (97%) of **80** as a pale orange oil. IR (thin film, NaCl) 3396 (br s), 3064 (w), 2922 (w), 2868 (w), 2233 (w), 1652 (w), 1559 (w), 1525 (s), 1490 (m), 1348 (m), 1033 (m), 961 (m), 757 (m), 691 (m); ^1H NMR (CDCl_3) δ 3.26 (d, J = 6 Hz, 1H), 6.21 (d, J = 6 Hz, 1H), 7.32 (m, 3H), 7.45 (m, 2H), 7.52 (dt, J = 1, 8 Hz, 1H), 7.70 (dt, J = 1, 8 Hz, 1H), 8.00 (dt, J

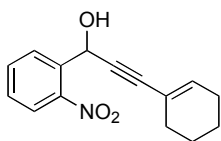
= 1, 8 Hz, 2H); ^{13}C NMR (CDCl_3) δ 62.0, 86.5, 86.9, 121.0, 125.1, 128.3, 128.8, 129.4, 129.6, 131.8, 133.8, 135.4, 148.2; HRMS (FAB^+ , $\text{M}+\text{Li}^+$) m/z for $\text{C}_{15}\text{H}_{11}\text{NO}_3\text{Li}^+$ calcd 260.0899, found 260.0896.

2-(2-Nitrophenyl)-4-phenyl-but-3-yn-2-ol **73**



Produced by the same procedure as **80**, using commercially available 2-nitroacetophenone. Column chromatography (4:1 hexanes/ethyl acetate, R_f = 0.26) yielded **73** as a pale orange oil (72%). IR (thin film, NaCl) 3527 (br s), 3081 (w), 3057 (w), 2989 (w), 2935 (w), 2883 (w), 2235 (w), 1598 (w), 1530 (s), 1490 (s), 1362 (s), 1070 (m), 854 (m), 757 (s), 691 (s); ^1H NMR (CDCl_3) δ 2.09 (s, 3H), 3.62 (s, 1H), 7.31 (m, 3H), 7.43 (m, 3H), 7.60 (m, 2H), 7.87 (dd, J = 1, 8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 30.9, 68.2, 84.8, 90.2, 121.8, 124.6, 127.3, 128.3, 128.7, 128.8, 131.8, 132.0, 137.8, 149.8; HRMS (FAB^+ , $\text{M}+\text{Li}^+$) m/z for $\text{C}_{16}\text{H}_{13}\text{NO}_3\text{Li}^+$ calcd 274.1055, found 274.1059.

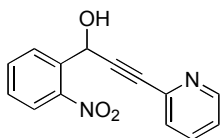
3-Cyclohexenyl-1-(2-nitrophenyl)-prop-2-yn-1-ol **81**



A solution of 1.18 mL (10.0 mmol) of 1-ethynylcyclohexene in 30 mL anhydrous THF was cooled to 0 °C, and 4.5 mL (9.0 mmol) of 2.0M *n*-butyl lithium was added dropwise. The resulting solution was stirred for 30 min at 0 °C, and warmed to room

temperature for an additional 30 min. After recooling to 0 °C, 1.340 g (8.87 mmol) of *o*-nitrobenzaldehyde dissolved in 5 mL anhydrous THF was added dropwise via cannula. The mixture was stirred at 0 °C for a subsequent 30 min, then quenched with water. The THF was removed *in vacuo*, and the residue was dissolved in diethyl ether, washed with water and saturated aqueous ammonium chloride, dried over MgSO₄ and concentrated *in vacuo*. Column chromatography (chloroform, R_f = 0.40) yielded 2.21g (97%) of **81** as a pale orange oil. IR (thin film, NaCl) 3528 (br s), 3416 (br s), 3111 (w), 3076 (w), 3028 (w), 2931 (s), 2859 (s), 2839 (m), 2218 (s), 1609 (m), 1529 (s), 1349 (m), 1180 (m), 1052 (s), 980 (m), 920 (m), 858 (m), 786 (m), 730 (m); ¹H NMR (CDCl₃) δ 1.59 (m, 4H), 2.10 (m, 4H), 3.15 (d, *J* = 6 Hz, 1H), 6.07 (d, *J* = 6 Hz, 1H), 6.15 (m, 1H), 7.49 (t, *J* = 8 Hz, 1H), 7.66 (t, *J* = 8 Hz, 1H), 7.93 (m, 2H); ¹³C NMR (CDCl₃) δ 21.3, 22.1, 25.6, 28.8, 61.8, 83.8, 88.8, 119.7, 124.9, 129.1, 129.5, 133.6, 135.7, 136.4, 148.2; HRMS (FAB⁺, M+Li⁺) *m/z* for C₁₅H₁₅NO₃Li⁺ calcd 264.1212, found 264.1217.

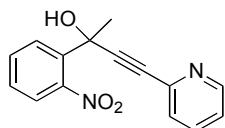
1-(2-Nitrophenyl)-3-(pyridin-2-yl)-prop-2-yn-1-ol **64**



A solution of 1.02 mL (10.0 mmol) of 2-ethynylpyridine in 30 mL anhydrous THF was cooled to 0 °C, and 4.5 mL (9.0 mmol) of 2.0M *n*-butyl lithium was added dropwise. The resulting solution was stirred for 30 min at 0 °C, and warmed to room temperature for an additional 30 min. After recooling to 0 °C, 1.27 g (8.40 mmol) of *o*-nitrobenzaldehyde dissolved in 5 mL anhydrous THF was added dropwise via

cannula. The mixture was stirred at 0 °C for a subsequent 30 min, then quenched with water. The THF was removed *in vacuo*, and the residue was dissolved in diethyl ether, washed with water and saturated aqueous ammonium chloride, dried over MgSO₄ and concentrated *in vacuo*. Column chromatography (diethyl ether, R_f = 0.18) yielded 380 mg (18%) of **64** as a pale orange oil. IR (thin film, NaCl) 3149 (br s), 2960 (w), 2935 (w), 2856 (w), 2253 (w), 2226 (w), 1588 (m), 1523 (s), 1471 (m), 1350 (m), 1057 (m), 1037 (m), 861 (m), 782 (m); ¹H NMR (CDCl₃) δ 5.33 (br s, 1H), 6.39 (s, 1H), 7.24 (m, 1H), 7.45 (m, 2H), 7.64 (m, 2H), 7.96 (dd, *J* = 1, 8 Hz, 1H), 8.10 (d, *J* = 7 Hz, 1H), 8.52 (d, *J* = 5 Hz, 1H); ¹³C NMR (CDCl₃) δ 60.6, 84.6, 88.6, 123.4, 124.8, 127.6, 129.0, 129.1, 133.7, 135.6, 136.7, 142.2, 147.8, 149.5; HRMS (FAB⁺, M+Li⁺) *m/z* for C₁₄H₁₀N₂O₃Li⁺ calcd 261.0851, found 261.0854.

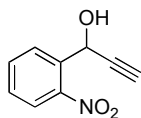
2-(2-Nitrophenyl)-4-(pyridin-2-yl)-but-3-yn-2-ol **83**



Produced by the same procedure as **64**, using commercially available 2-nitroacetophenone. Column chromatography (7:3 hexanes/ethyl acetate, R_f = 0.06) yielded **83** as a pale orange oil (59%). IR (thin film, NaCl) 3154 (br s), 2990 (m), 2934 (m), 2866 (w), 2806 (w), 2245 (w), 1589 (s), 1529 (s), 1468 (m), 1362 (m), 1280 (m), 1153 (m), 1110 (m), 908 (m), 855 (s), 780 (s), 738 (s); ¹H NMR (CDCl₃) δ 2.10 (s, 3H), 4.60 (br s, 1H), 7.22 (m, 1H), 7.43 (m, 2H), 7.55-7.66 (m, 3H), 7.92 (d, *J* = 8 Hz, 1H), 8.50 (d, *J* = 4 Hz, 1H); ¹³C NMR (CDCl₃) δ 31.3, 68.3, 83.6, 90.7,

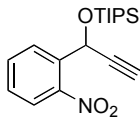
123.2, 124.4, 127.6, 127.7, 128.8, 131.9, 136.4, 137.7, 142.2, 149.5, 149.7; HRMS (FAB⁺, M+H⁺) *m/z* for C₁₅H₁₃N₂O₃⁺ calcd 269.0926, found 269.0918.

1-(2-Nitrophenyl)-prop-2-yn-1-ol **59**



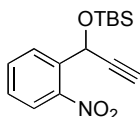
A solution of 1.00 g (6.62 mmol) of *o*-nitrobenzaldehyde in 40 mL anhydrous THF was cooled to 0 °C, and 17.6 mL (8.80 mmol) of 0.5M ethynylmagnesium bromide solution was added dropwise. The resulting solution was stirred for 20 min at 0 °C, then quenched with water. The THF was removed *in vacuo*, and the residue was dissolved in diethyl ether, washed with water and brine, dried over MgSO₄ and concentrated *in vacuo*. Radial chromatography (7:3 hexanes/ethyl acetate, R_f = 0.25) and recrystallization from chloroform yielded 1.13 g (96%) of **59** as an off-white solid, mp 54.0-55.5 °C. IR (thin film, NaCl) 3530 (br s), 3416 (br s), 3290 (s), 3109 (w), 2927 (w), 2866 (w), 2121 (m), 1610 (m), 1579 (m), 1527 (s), 1349 (s), 1031 (s); ¹H NMR (CDCl₃) δ 2.65 (s, 1H), 3.24 (br s, 1H), 6.02 (s, 1H), 7.52 (dt, *J* = 1, 8 Hz, 1H), 7.69 (dt, *J* = 1, 8 Hz, 1H), 7.98 (dt, *J* = 1, 8 Hz, 2H); ¹³C NMR (CDCl₃) δ 60.8, 75.0, 81.4, 124.9, 129.1, 129.3, 133.8, 134.8, 147.7; Anal. calcd for C₉H₇NO₃: C, 61.02; H, 3.98; N, 7.91, found: C, 61.27; H, 3.97; N, 7.89.

Triisopropyl-(1-(2-nitrophenyl)-prop-2-ynyloxy)-silane **61**



To a solution of 744 mg (4.20 mmol) of **59**, and 872 mg (12.6 mmol) of imidazole in 10 mL anhydrous CH_2Cl_2 was added 2.70 mL (12.6 mmol) of triisopropylsilyl chloride, and the solution was stirred at room temperature for 22 hours. The mixture was dissolved in diethyl ether, washed with water and brine, dried over MgSO_4 concentrated *in vacuo*. Recrystallization of the crude residue from pentane gave 1.19 g (85%) of **61** as a pale orange solid, mp 57.5-58.5 °C. IR (thin film, NaCl) 3311 (m), 2946 (s), 2868 (s), 1533 (s), 1464 (w), 1351 (m), 1100 (m), 1065 (m), 883 (m); ^1H NMR (CDCl_3) δ 1.06 (d, $J = 7$ Hz, 9H), 1.11 (d, $J = 7$ Hz, 9H), 1.21 (m, 3H), 2.46 (d, $J = 2$ Hz, 1H), 6.32 (d, $J = 2$ Hz, 1H), 7.46 (dt, $J = 1, 8$ Hz, 1H), 7.68 (dt, $J = 1, 8$ Hz, 1H), 8.00 (dd, $J = 1, 8$ Hz, 1H), 8.06 (d, $J = 8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 12.1, 17.9, 60.5, 73.0, 83.1, 124.6, 127.9, 128.5, 133.7, 137.5, 146.7; Anal. calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_3\text{Si}$: C, 64.83; H, 8.16; N, 4.20, found: C, 64.92; H, 8.12; N, 4.21.

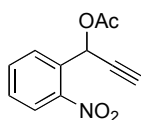
tert-Butyldimethyl-(1-(2-nitrophenyl)-prop-2-ynyloxy)-silane **62**



A solution of 3.00 g (19.9 mmol) of *o*-nitrobenzaldehyde in 100 mL anhydrous THF was cooled to 0 °C, and 51.6 mL (25.8 mmol) of 0.5M ethynylmagnesium bromide was added dropwise. The resulting solution was stirred for 1h at 0 °C, then quenched with water. The THF was removed *in vacuo*, and the residue was dissolved in

diethyl ether, washed with water and saturated aqueous NaHCO₃, dried over MgSO₄ and concentrated *in vacuo*. The residue was then dissolved in 50 mL of CH₂Cl₂, and both 3.38 g (49.6 mmol) of imidazole and 3.59 g (23.8 mmol) of *tert*-butyldimethylsilyl chloride were added. The resulting mixture was stirred for 1h at room temperature, then washed with water, dried over MgSO₄, and concentrated *in vacuo*. Column chromatography (4:1 hexanes/ethyl acetate, R_f = 0.54) yielded 5.67 g (97 %) of **62** as a pale orange oil. IR (thin film, NaCl) 3299 (s), 3105 (w), 3082 (w), 2956 (s), 2930 (s), 2886 (m), 2858 (s), 2119 (w), 1609 (w), 1579 (w), 1532 (s), 1472 (m), 1352 (s), 1255 (s), 1099 (s), 1069 (s), 841 (s), 781(s); ¹H NMR (CDCl₃) δ 0.17 (s, 3H), 0.22 (s, 3H), 0.94 (s, 9H), 2.49 (d, *J* = 2 Hz, 1H), 6.22 (d, *J* = 2 Hz, 1H), 7.47 (dt, *J* = 1, 8 Hz, 1H), 7.67 (dt, *J* = 1, 8 Hz, 1H), 7.97 (dd, *J* = 1, 8 Hz, 1H), 8.01 (d, *J* = 8 Hz, 1H); ¹³C NMR (CDCl₃) δ -5.2, -4.7, 18.2, 25.7, 60.7, 73.6, 82.8, 124.6, 128.0, 128.6, 133.5, 136.7, 147.0; HRMS (FAB⁺, M+Li⁺) *m/z* for C₁₅H₂₂NO₃SiLi⁺ calcd 292.1369, found 292.1363.

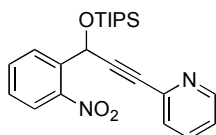
1-(2-Nitrophenyl)-prop-2-ynyl ethanoate **63**



A solution of 3.00 g (19.9 mmol) of *o*-nitrobenzaldehyde in 100 mL anhydrous THF was cooled to 0 °C, and 51.6 mL (25.8 mmol) of 0.5M ethynylmagnesium bromide was added dropwise. The resulting solution was stirred for 1h at 0 °C, then quenched with water. The THF was removed *in vacuo*, and the residue was dissolved in diethyl ether, washed with water and saturated aqueous NaHCO₃, dried over MgSO₄ and

concentrated *in vacuo*. The residue was dissolved in 50 mL of CHCl_3 , and both 4.76 mL (59.6 mmol) of pyridine and 2.44 mL (25.8 mmol) of acetic anhydride were added. After the resulting mixture was stirred for 3h at room temperature, TLC showed incomplete protection, so acetic anhydride and pyridine were added (same amounts). After another 2.5h, a third portion of acetic anhydride was required to complete the conversion. The reaction mixture was concentrated *in vacuo*, dissolved with diethyl ether, washed with water, dried over MgSO_4 , and concentrated *in vacuo*. Column chromatography (4:1 hexanes/ethyl acetate, $R_f = 0.24$) yielded 3.71 g (85 %) of **63** as a pale orange solid, mp 60.0-61.0 °C. IR (thin film, NaCl) 3290 (s), 3110 (w), 3081 (w), 3041 (w), 2870 (w), 2128 (m), 1751 (s), 1539 (s), 1350 (s), 1220 (s), 1022 (s), 962 (s), 857 (s), 787 (s); ^1H NMR (CDCl_3) δ 2.12 (s, 3H), 2.68 (d, $J = 2$ Hz, 1H), 7.04 (d, $J = 2$ Hz, 1H), 7.55 (dt, $J = 1, 8$ Hz, 1H), 7.70 (dt, $J = 1, 8$ Hz, 1H), 7.94 (d, $J = 8$ Hz, 1H), 8.01 (d, $J = 8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 20.5, 61.5, 76.1, 78.7, 124.9, 129.3, 129.8, 131.4, 133.6, 169.0; Anal. calcd for $\text{C}_{11}\text{H}_9\text{NO}_4$: C, 60.27; H, 4.14; N, 6.39, found: C, 60.40; H, 4.29; N, 6.41.

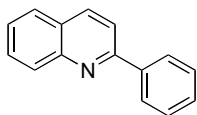
2-(3-(2-Nitrophenyl)-3-(triisopropylsilyloxy)-prop-1-ynyl)-pyridine **65**



A solution of 200 mg (0.600 mmol) of **61**, 0.10 mL (0.66 mmol) of 2-pyridyl triflate, 14 mg (0.012 mmol) of tetrakis(triphenylphosphine) palladium(0), 2.3 mg (0.012 mmol) of copper(I) iodide, and 0.21 mL (1.5 mmol) of triethylamine in 5 mL anhydrous THF was stirred at room temperature for 16h. The crude mixture was

filtered through Celite, concentrated *in vacuo*, dissolved in diethyl ether, washed with water and brine, dried with MgSO_4 , and concentrated *in vacuo*. Radial chromatography (7:3 hexanes/ethyl acetate, $R_f = 0.47$) yielded 199 mg (81%) of **65** as a pale orange oil. IR (thin film, NaCl) 3076 (w), 3053 (w), 2945 (s), 2892 (m), 2867 (s), 1582 (m), 1529 (s), 1464 (s), 1428 (m), 1351 (s), 1099 (s), 1064 (s), 883 (m), 780 (m), 680 (m); ^1H NMR (CDCl_3) δ 1.09 (d, $J = 7$ Hz, 9H), 1.13 (d, $J = 7$ Hz, 9H), 1.26 (m, 3H), 6.56 (s, 1H), 7.19 (m, 1H), 7.37 (d, $J = 8$ Hz, 1H), 7.45 (dt, $J = 1, 8$ Hz, 1H), 7.60 (dt, $J = 2, 8$ Hz, 1H), 7.69 (dt, $J = 1, 8$ Hz, 1H), 8.00 (dd, $J = 1, 8$ Hz, 1H), 8.12 (dd, $J = 1, 8$ Hz, 1H), 8.52 (d, $J = 4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 12.1, 17.9, 61.0, 84.0, 88.4, 122.9, 124.6, 127.4, 128.3, 128.5, 133.7, 136.0, 137.3, 142.7, 146.6, 149.9; HRMS (FAB^+ , $\text{M}+\text{H}^+$) m/z for $\text{C}_{23}\text{H}_{31}\text{N}_2\text{O}_3\text{Si}^+$ calcd 411.2104, found 411.2112.

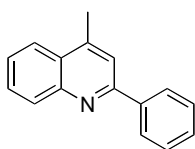
2-Phenylquinoline **88**



A solution of 195 mg (3.49 mmol) of iron metal in 4 mL ethanol was heated to 80 °C, then 2 drops of concentrated HCl were added. The mixture was stirred for 1h, then 184 mg (0.727 mmol) of **80** dissolved in 4 mL ethanol was added, and stirred at 80 °C until the starting material was consumed, an additional 2h. Then 1 mL of 10% aq. HCl was added, and the mixture stirred for an additional 25h, adding additional 1 mL aliquots of aq. HCl if the pH > 4. The reaction mixture was quenched with saturated aqueous NaHCO_3 , dissolved in diethyl ether, washed with saturated, basic aqueous

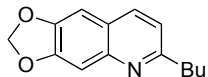
EDTA, dried with MgSO₄, and concentrated *in vacuo*. The resulting residue was redissolved in ether, washing with five 20 mL portions of 2% aq. HCl. The combined aqueous layers were basified with solid NaHCO₃, extracted with diethyl ether, dried with MgSO₄, and concentrated *in vacuo*, yielding 96 mg (64%) of **88** as a white solid, mp 78.0-79.0 °C. ¹H NMR (CDCl₃) δ 7.47 (m, 1H), 7.54 (m, 3H), 7.74 (m, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.88 (d, *J* = 8 Hz, 1H), 8.17-8.24 (m, 4H); ¹³C NMR (CDCl₃) δ 119.0, 126.3, 127.2, 127.5, 127.6, 128.8, 129.3, 129.6, 129.8, 136.8, 139.7, 148.3, 157.4; characterization data matched those reported by Miyaura.²⁰⁰

4-Methyl-2-phenylquinoline **75**



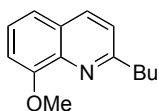
Produced by the same procedure as **88**, using propargyl alcohol **73**. Column chromatography (9:1 hexanes/ethyl acetate, *R_f* = 0.42) yielded **75** as a pale yellow oil (82%). IR (thin film, NaCl) 3061 (m), 3035 (w), 2979 (w), 2951 (w), 2921 (w), 1598 (s), 1551 (s), 1509 (m), 1495 (m), 1451 (s), 1349 (s), 769 (s), 694 (s); ¹H NMR (CDCl₃) δ 2.76 (s, 3H), 7.48 (m, 1H), 7.55 (m, 3H), 7.72 (m, 2H), 8.00 (d, *J* = 8 Hz, 1H), 8.20 (m, 3H); ¹³C NMR (CDCl₃) δ 18.9, 119.7, 123.5, 125.9, 127.2, 127.5, 128.7, 129.1, 129.2, 130.2, 139.8, 144.7, 148.1, 157.0; HRMS (EI⁺, M⁺) *m/z* for C₁₆H₁₃N⁺ calcd 219.1048, found 219.1053.

2-Butyl-6,7-methylenedioxyquinoline **85**



Produced by the same procedure as **88**, using propargyl alcohol **77**. Crude residue was dissolved in hexane, and filtered. Kugelrohr distillation (175 °C, 10 mm Hg), yielded **85** as a pale orange solid (82%), mp 84.5-85.5 °C. IR (thin film, NaCl) 3042 (w), 2957 (m), 2928 (m), 2856 (m), 1619 (m), 1514 (m) 1464 (s), 1240 (s), 1037 (m), 940 (m), 853 (s), 733 (s); ¹H NMR (CDCl₃) δ 0.96 (t, *J* = 8 Hz, 3H), 1.43 (m, 2H), 1.76 (m, 2H), 2.90 (t, *J* = 8 Hz, 2H), 6.08 (s, 2H), 7.02 (s, 1H), 7.14 (d, *J* = 8 Hz, 1H), 7.34 (s, 1H), 7.86 (d, *J* = 8 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.0, 22.7, 32.3, 38.8, 101.5, 102.6, 105.6, 119.5, 123.3, 135.0, 146.1, 147.1, 150.5, 160.8; HRMS (FAB⁺, M+H⁺) *m/z* for C₁₄H₁₆NO₂⁺ calcd 230.1181, found 230.1184.

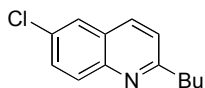
2-Butyl-8-methoxyquinoline **87**



Produced by the same procedure as **88**, using propargyl alcohol **79**. After acid/base extraction (same as 2-phenylquinoline), Kugelrohr distillation (175 °C, 10 mm Hg) yielded **87** as a pale yellow oil (44%). IR (thin film, NaCl) 3048 (w), 3000 (w), 2955 (s), 2930 (s), 2871 (m), 2858 (m), 2834 (m), 1615 (m), 1603 (s), 1564 (s), 1503 (s), 1472 (s), 1428 (s), 1378 (m), 1323 (m), 1259 (s), 1111 (s), 998 (m), 833 (m), 751 (m); ¹H NMR (CDCl₃) δ 0.96 (t, *J* = 8 Hz, 3H), 1.45 (m, 2H), 1.80 (m, 2H), 3.03 (t, *J* = 8 Hz, 2H), 4.07 (s, 3H), 7.02 (d, *J* = 8 Hz, 1H), 7.36 (m, 3H), 8.01 (d, *J* = 8 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.2, 23.0, 32.5, 39.5, 56.2, 107.8, 119.6, 121.9, 125.8, 128.0,

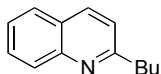
136.2, 139.9, 155.1, 162.4; HRMS (FAB⁺, M+H⁺) *m/z* for C₁₄H₁₈NO⁺ calcd 216.1388, found 216.1389.

2-Butyl-6-chloroquinoline **86**



Produced by the same procedure as **88**, using propargyl alcohol **78**. Crude residue was dissolved in hexane, and filtered. Kugelrohr distillation (180 °C, 10 mm Hg), yielded **86** as a pale yellow oil (68%). IR (thin film, NaCl) 3055 (w), 2957 (s), 2929 (s), 2871 (m), 2859 (m), 1599 (s), 1489 (s), 1073 (m), 876 (m), 831 (s); ¹H NMR (CDCl₃) δ 0.98 (t, *J* = 8 Hz, 3H), 1.45 (m, 2H), 1.79 (m, 2H), 2.96 (m, 2H), 7.31 (d, *J* = 8 Hz, 1H), 7.61 (dd, *J* = 4, 8 Hz, 1H), 7.75 (d, *J* = 4 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.0, 22.6, 32.0, 39.0, 122.2, 126.1, 127.2, 130.1, 130.4, 131.2, 135.2, 146.3, 163.5; HRMS (FAB⁺, M+H⁺) *m/z* for C₁₃H₁₅ClN⁺ calcd 220.0901, found 220.0893.

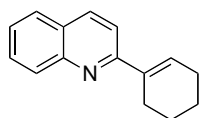
2-Butylquinoline **84**



A solution of 677 mg (2.90 mmol) of propargyl alcohol **76**, 1.40 g (21.4 mmol) of zinc dust, 247 mg (4.62 mmol) of ammonium chloride in 15 mL ethanol/water (2:1 v/v) was stirred at 85 °C for 4h. Then 3 mL of glacial acetic acid was added, and the solution stirred for an additional 2h. The reaction mixture was quenched with saturated aqueous NaHCO₃, dissolved in diethyl ether, washed with water, dried with

MgSO₄, and concentrated *in vacuo*. The resulting residue was redissolved in pentane, filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in diethyl ether, and washed with five 20 mL portions of 2% aq. HCl. The combined aqueous layers were basified with solid NaHCO₃, extracted with ethyl acetate, dried with MgSO₄, and concentrated *in vacuo*, yielding 426 mg (79%) of **84** as a pale yellow oil. IR (thin film, NaCl) 3057 (w), 2956 (s), 2929 (s), 2871 (m), 2859 (m), 1617 (m), 1601 (s), 1503 (s), 1426 (m), 1310 (w), 1116 (w), 826 (s), 756 (s); ¹H NMR (CDCl₃) δ 0.97 (t, *J* = 8 Hz, 3H), 1.44 (m, 2H), 1.80 (m, 2H), 3.00 (t, *J* = 8 Hz, 2H), 7.30 (m, 1H), 7.48 (m, 1H), 7.68 (m, 1H), 7.78 (d, *J* = 8 Hz, 1H), 8.05 (m, 2H); ¹³C NMR (CDCl₃) δ 14.0, 22.7, 32.2, 39.1, 121.3, 125.6, 126.7, 127.4, 128.8, 129.3, 136.1, 147.9, 163.1; HRMS (FAB⁺, M+H⁺) *m/z* for C₁₃H₁₆N⁺ calcd 186.1283, found 186.1284.

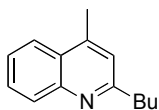
2-Cyclohexenylquinoline **89**



Produced by the same procedure as **84**, using propargyl alcohol **81**. Crude residue dissolved in hexanes and filtered. Kugelrohr distillation (165 °C, 0.5 mm Hg) yielded **89** as a pale orange oil (34%). IR (thin film, NaCl) 3059 (m), 3037 (m), 2928 (s), 2856 (s), 2830 (m), 1616 (m), 1598 (s), 1504 (s), 1428 (m), 1311 (w), 1231 (m), 820 (s), 754 (s); ¹H NMR (CDCl₃) δ 1.73 (m, 2H), 1.85 (m, 2H), 2.33 (m, 2H), 2.72 (m, 2H), 6.78 (m, 1H), 7.46 (t, *J* = 8 Hz, 1H), 7.57 (d, *J* = 8 Hz, 1H), 7.66 (dt, *J* = 1 & 8 Hz, 1H), 7.75 (d, *J* = 8 Hz, 1H), 8.06 (t, *J* = 9 Hz, 2H); ¹³C NMR (CDCl₃) δ 22.3,

23.0, 26.2, 26.3, 118.1, 125.8, 127.1, 127.4, 129.4, 129.6, 130.5, 136.0, 137.9, 147.9, 159.4; HRMS (FAB⁺, M+H⁺) *m/z* for C₁₅H₁₆N⁺ calcd 210.1283, found 210.1286.

2-Butyl-4-methylquinoline **74**

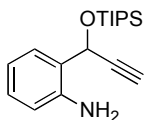


Tin Reduction: A solution of 269 mg (1.09 mmol) of propargyl alcohol **72** and 736 mg (3.26 mmol) of tin(II) chloride monohydrate in 6 mL ethanol was stirred at 80 °C for 2.5h. Then 5 drops of concentrated HCl was added, and the solution stirred for an additional 2h. The reaction mixture was quenched with saturated aqueous NaHCO₃, dissolved in diethyl ether, washed with water, dried with MgSO₄, and concentrated *in vacuo*. Filtration through a short column of silica gel with 7:3 hexanes/ethyl acetate yielded 197 mg (91%) of **74** as a pale yellow oil.

Zinc Reduction: A solution of 243 mg (0.98 mmol) of propargyl alcohol **72**, 450 mg (6.88 mmol) of zinc dust, 168 mg (3.14 mmol) of ammonium chloride in 6 mL ethanol/water (2:1 v/v) was stirred at 85 °C for 2.5h. Then 1 mL of glacial acetic acid was added, and the solution stirred for an additional 1h. The reaction mixture was quenched with saturated aqueous NaHCO₃, dissolved in diethyl ether, washed with water, dried with MgSO₄, and concentrated *in vacuo*. Filtration through a short column of silica gel with 7:3 hexanes/ethyl acetate yielded 186 mg (95%) of **74** as a pale yellow oil. IR (thin film, NaCl) 3061 (w), 3033 (w), 2956 (s), 2929 (s), 2871 (m), 2859 (m), 1604 (s), 1562 (m), 1508 (m), 1448 (m), 758 (s) ¹H NMR (CDCl₃) δ 0.97 (t, 3H, *J* = 8 Hz), 1.44 (m, 2H), 1.80 (m, 2H), 2.68 (s, 3H), 2.92 (t, 2H, *J* = 8

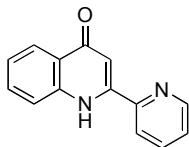
Hz), 7.15 (s, 1H), 7.50 (m, 1H), 7.67 (m, 1H), 7.94 (d, $J = 8$ Hz, 1H), 8.04 (d, $J = 8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 13.9, 18.6, 22.7, 32.1, 38.9, 122.0, 123.5, 125.3, 126.7, 128.9, 129.3, 144.0, 147.7, 162.7; HRMS (EI^+ , M^+) m/z for $\text{C}_{14}\text{H}_{17}\text{N}^+$ calcd 199.1361, found 199.1360.

2-(1-(Triisopropylsilyloxy)prop-2-ynyl)aniline **67**



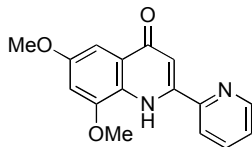
A solution of 100 mg (1.79 mmol) of iron metal in 3 mL ethanol was heated to 80 °C, then 2 drops of concentrated HCl were added. The mixture was stirred for 1h, then 119 mg (0.357 mmol) of **61** and 0.75 mL of saturated aqueous ammonium chloride were added, and stirred at 80 °C for an additional 19h. The reaction mixture was quenched with saturated aqueous NaHCO_3 , dissolved in diethyl ether, washed with water, dried with MgSO_4 , and concentrated *in vacuo*. Radial chromatography (chloroform) yielded 36 mg (33%) of **67** as a pale orange oil. ^1H NMR (CDCl_3) δ 1.05 (d, 9H, $J = 7$ Hz), 1.10 (d, 9H, $J = 7$ Hz), 1.16 (m, 3H), 2.55 (s, 1H), 4.36 (br s, 2H), 5.49 (s, 1H), 6.69 (m, 2H), 7.10 (m, 2H); ^{13}C NMR (CDCl_3) δ 12.1, 17.8, 65.2, 72.9, 83.4, 116.7, 117.8, 125.1, 127.5, 129.0, 144.9; HRMS (EI^+ , M^+) m/z for $\text{C}_{18}\text{H}_{29}\text{NOSi}^+$ calcd 303.2018, found 303.2015.

2-(Pyridin-2-yl)quinolin-4(1H)-one **90**



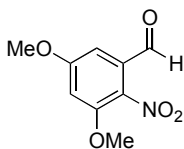
A solution of 55 mg (1.0 mmol) of iron metal in 2 mL ethanol was heated to 80 °C, then 2 drops of concentrated HCl were added. The mixture was stirred for 1h, then 81 mg (0.20 mmol) of **64** dissolved in 2 ml of ethanol and 1.0 mL of saturated aqueous ammonium chloride were added, and stirred at 80 °C for an additional 35h. The reaction mixture was quenched with saturated aqueous NaHCO₃, dissolved in diethyl ether, washed with water, dried with MgSO₄, and concentrated *in vacuo*. Radial chromatography (7:3 hexanes/ethyl acetate, R_f = 0.41) yielded 23 mg (53%) of **90** as an orange solid. IR (CCl₄) 3354 (w), 3053 (w), 3010 (w), 2954 (w), 2923 (w), 2855 (w), 2289 (m), 1707 (s), 1614 (s), 1549 (s), 1483 (s), 1469 (s), 1383 (m), 1253 (s), 1217 (s), 1005 (m), 979 (m), 827 (br s); ¹H NMR (CDCl₃) δ 6.61 (s, 1H), 6.90 (t, 1H, *J* = 8 Hz), 6.97 (d, 1H, *J* = 8 Hz), 7.15 (m, 1H), 7.38 (d, 1H, *J* = 8 Hz), 7.45 (t, 1H, *J* = 7 Hz), 7.68 (m, 2H), 8.66 (d, 1H, *J* = 4 Hz), 9.95 (br s, 1H); ¹³C NMR (CDCl₃) δ 105.3, 111.6, 120.2, 120.9, 121.6, 125.2, 126.3, 136.6, 136.7, 138.4, 149.4, 153.3, 156.1, 187.9; HRMS (EI⁺, M⁺) *m/z* for C₁₄H₁₀N₂O⁺ calcd 222.0793, found 222.0794; characterization data matched those reported by Jahng.²⁰¹

6,8-Dimethoxy-2-(pyridin-2-yl)quinolin-4(1H)-one **117**



A solution of 135 mg (2.42 mmol) of iron metal in 3 mL ethanol was heated to 80 °C, then 2 drops of concentrated HCl were added. The mixture was stirred for 30 min, then 44 mg (0.14 mmol) of **96** was added, and stirred at 80 °C for an additional 12h. The reaction mixture was quenched with saturated, basic aqueous EDTA, dissolved in ethyl acetate, washed with basic EDTA, dried with MgSO₄, and concentrated *in vacuo*. Filtration of the crude reaction mixture through a short column of silica with 1:1 ethyl acetate:hexanes yielded 31 mg (78%) of **117** as a purple powder. IR (thin film, NaCl) 3381 (m), 3009 (w), 2925 (m), 1695 (s), 1620 (s), 1508 (s), 1468 (m), 1439 (m), 1381 (s), 1279 (m), 1255 (m), 1150 (m), 1130 (s), 1044 (m), 933 (w), 781(m); ¹H NMR (CDCl₃) δ 3.78 (s, 3H), 3.92 (s, 3H), 6.64 (m, 2H), 6.76 (d, 1H, *J* = 2 Hz), 7.14 (m, 1H), 7.38 (d, 1H, *J* = 8 Hz), 7.66 (m, 1H), 8.69 (d, 1H, *J* = 5 Hz), 9.56 (br s, 1H); ¹³C NMR (CDCl₃) δ 55.9, 56.0, 96.8, 106.5, 107.6, 120.7, 121.6, 126.3, 136.5, 138.8, 140.0, 146.4, 149.6, 154.8, 156.0, 188.0.

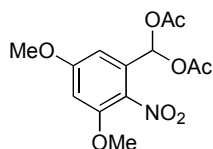
3,5-Dimethoxy-2-nitrobenzaldehyde **102**



A mixture of 500 mg of claycop (cupric nitrate on Montmorillonite clay, prepared by the Laszlo procedure¹⁹³), 1 mL (10.6 mmol) of acetic anhydride, 173 mg (1.03 mmol)

of 3,5-dimethoxybenzaldehyde, and 10 drops of conc. HNO_3 in 5 mL of diethyl ether was stirred at room temperature for 1.5h. By TLC, starting material was not fully consumed, so an additional 10 drops of HNO_3 was added, and the mixture stirred for an additional 1.5h. The reaction mixture was filtered through a short column of silica with diethyl ether, then washed with water, dried with MgSO_4 , and concentrated *in vacuo*. This crude residue was primarily **102**, with some gem-diacetate **104** also. The mixture was dissolved in chloroform, and ~ 10g of silica gel and 1 mL of 3N H_2SO_4 were added. This mixture was stirred at room temperature for 6h, then filtered, washed with water, and concentrated *in vacuo*. Column chromatography (chloroform), followed by recrystallization from hexanes yielded 191 mg (87%) of **102** as an off-white solid, mp 97.0-99.0 °C. IR (thin film, NaCl) 3308 (w), 3018 (w), 2978 (w), 2943 (w), 2892 (w), 2845 (w), 1703 (s), 1589 (s), 1534 (s), 1462 (m), 1340 (m), 1311 (m), 1201 (m), 1038 (w), 959 (m), 842 (s); ^1H NMR (CDCl_3) δ 3.92 (s, 3H), 3.94 (s, 3H), 6.77 (d, 1H, $J = 2$ Hz), 6.97 (d, 1H, $J = 2$ Hz), 9.95 (s, 1H); ^{13}C NMR (CDCl_3) δ 56.2, 56.8, 104.3, 104.8, 130.5, 135.4, 153.2, 162.1, 186.8. Characterization data matched those reported by Chang.¹⁹²

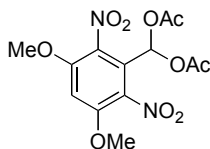
Gem-diacetate of 3,5-dimethoxy-2-nitrobenzaldehyde **104**



Produced by the same procedure as **102**, without the HNO_3 . Column chromatography (7:3 hexanes/ethyl acetate, $R_f = 0.17$) yielded **104** (24%) as a white solid. IR (thin film, NaCl) 3102 (w), 2959 (m), 2924 (s), 2853 (s), 1766 (m), 1597 (m), 1529 (m),

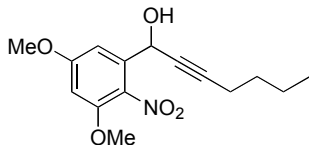
1462 (m), 1366 (m), 1204 (m), 1015 (m); ^1H NMR (CDCl_3) δ 2.12 (s, 6H), 3.87 (s, 3H), 3.89 (s, 1H), 6.56 (d, 1H, $J = 2$ Hz), 6.60 (d, 1H, $J = 2$ Hz), 7.72 (s, 1H); ^{13}C NMR (CDCl_3) δ 20.6, 56.0, 56.8, 86.6, 100.4, 103.9, 130.8, 133.8, 153.4, 161.7, 168.4.

Gem-diacetate of 3,5-dimethoxy-2,6-dinitrobenzaldehyde **107**



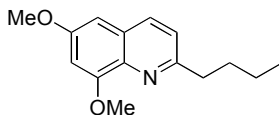
A mixture of 64 mg of claycop, 0.25 mL (2.7 mmol) of acetic anhydride, 42 mg (0.13 mmol) of **104** in 1 mL of diethyl ether was stirred at room temperature for 16h. The reaction mixture was filtered through a short column of silica with diethyl ether, then washed with water, dried with MgSO_4 , and concentrated *in vacuo*. This crude residue was primarily unreacted **104**, however, column chromatography (1:1 hexanes/ethyl acetate) yielded trace amounts of **107**. Regiochemistry of second nitro group unconfirmed, but inferred from symmetry of NMR spectra. IR (thin film, NaCl) 3114 (w), 3026 (w), 2925 (s), 2853 (m), 1781 (s), 1601 (s), 1545 (s), 1437 (m), 1364 (s), 1223 (s), 1192 (s), 1066 (m), 1017 (s), 831 (m), 760 (m); ^1H NMR (CDCl_3) δ 2.09 (s, 6H), 3.98 (s, 6H), 6.67 (s, 1H), 7.64 (s, 1H); ^{13}C NMR (CDCl_3) δ 20.2, 57.1, 84.0, 97.9, 123.3, 132.7, 153.4, 167.8.

1-(3,5-Dimethoxy-2-nitrophenyl)hept-2-yn-1-ol **105**



Produced by the same procedure as **76**, using 3,5-dimethoxy-2-nitrobenzaldehyde **102**. Column chromatography (chloroform, $R_f = 0.20$) yielded **105** as a pale brown oil (77%). IR (thin film, NaCl) 3516 (br s), 3102 (w), 2955 (s), 2936 (s), 2873 (s), 2285 (w), 2235 (m), 1610 (s), 1536 (m), 1464 (m), 1330 (m), 1202 (m), 1167 (m), 1119 (m), 1012 (m), 929 (m), 844 (s); ^1H NMR (CDCl_3) δ 0.86 (t, 3H, $J = 7$ Hz), 1.36 (m, 2H), 1.46 (m, 2H), 2.20 (t, 2H, $J = 7$ Hz), 3.83 (s, 6H), 5.55 (m, 1H), 6.45 (d, 1H, $J = 2$ Hz), 6.83 (d, 1H, $J = 2$ Hz); ^{13}C NMR (CDCl_3) δ 13.6, 18.4, 22.0, 30.4, 55.8, 56.6, 61.2, 77.5, 88.3, 99.3, 103.9, 133.7, 136.7, 153.3, 161.8.

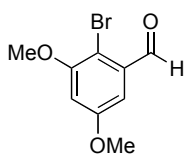
2-Butyl-6,8-dimethoxyquinoline **106**



A solution of 440 mg (7.88 mmol) of iron metal in 5 mL ethanol was heated to 80 °C, then 5 drops of concentrated HCl were added. The mixture was stirred for 30 min, then 292 mg (1.00 mmol) of **105** dissolved in 3 mL ethanol was added, and stirred at 80 °C for 20h. The reaction mixture was quenched with saturated aqueous NaHCO_3 , dissolved in diethyl ether, washed with saturated, basic aqueous EDTA, dried with MgSO_4 , and concentrated *in vacuo*. The residue was dissolved in chloroform, and washed with five 20 mL portions of 5% aq. HCl. The combined aqueous layers were basified with aqueous 0.5M NaOH, and extracted three times with diethyl ether. The

combined ether layers were dried with MgSO_4 , and concentrated *in vacuo*, yielding 200 mg (82%) of **106** as a pale yellow oil. IR (thin film, NaCl) 3009 (m), 2956 (s), 2932 (s), 2871 (m), 2858 (m), 1625 (s), 1621 (s), 1614 (s), 1570 (s), 1466 (m), 1386 (m), 1201 (s), 1122 (s), 1051 (m), 839 (s); ^1H NMR (CDCl_3) δ 0.93 (t, 3H, $J = 7$ Hz), 1.42 (m, 2H), 1.75 (m, 2H), 2.96 (t, 2H, $J = 8$ Hz), 3.87 (s, 3H), 4.01 (s, 3H), 6.60 (d, 1H, $J = 2$ Hz), 6.67 (d, 1H, $J = 2$ Hz), 7.26 (d, 1H, $J = 8$ Hz), 7.88 (d, 1H, $J = 8$ Hz); ^{13}C NMR (CDCl_3) δ 14.1, 22.9, 32.4, 39.0, 55.5, 56.2, 96.9, 101.1, 122.1, 128.3, 135.1, 136.3, 155.9, 157.5, 159.7.

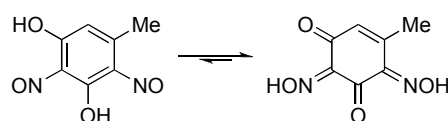
2-Bromo-3,5-dimethoxybenzaldehyde **108**



A solution of 1.33 g (8.00 mmol) of 3,5-dimethoxybenzaldehyde in 40 mL of methanol and 60 mL of methylene chloride was stirred at room temperature, then a solution of 3.90 g (8.00 mmol) tetrabutylammonium tribromide in 10 mL of the same 2:3 MeOH/ CH_2Cl_2 solution was added dropwise. After addition, this mixture stirred at room temperature for 24h. The crude reaction mixture was extracted with ethyl acetate, washed with water, dried with MgSO_4 , and concentrated *in vacuo*. Crude NMR showed a 2:1 mixture of **108** and its dimethyl acetal, so the crude residue was dissolved in CH_2Cl_2 , and 3.3 g of Montmorillonite K-10 clay was added. This mixture stirred for 10 min, until the dimethyl acetal was no longer observed by TLC (CHCl_3 , $R_f = 0.36$), then filtered through Celite, and concentrated *in vacuo*. Recrystallization from hexanes yielded 1.85 g (94%) of **108** as white crystals, mp

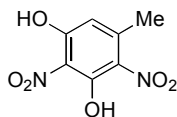
105.0-106.0 °C. ^1H NMR (CDCl_3) δ 3.84 (s, 3H), 3.90 (s, 3H), 6.69 (d, 1H, $J = 3$ Hz), 7.02 (d, 1H, $J = 3$ Hz), 10.39 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.8, 56.6, 103.4, 105.8, 109.1, 134.7, 157.0, 159.9, 192.0. Anal. calcd for $\text{C}_9\text{H}_9\text{BrO}_3$: C, 44.11; H, 3.70, found: C, 44.32; H, 3.76. Characterization data matched those from past reports.²⁰²⁻²⁰⁴

2,4-Dinitrosoorcinol **112**



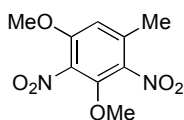
A solution of 4.97 g (35.0 mmol) of orcinol monohydrate in 84 mL of 0.5M NaOH was cooled to 0 °C, then 4.90 g (70 mmol) of sodium nitrite was added, followed by the slow dropwise addition of 37.5 mL of 6M H_2SO_4 over 1h. Early drops added ca. 5/min. Visible evolution of brown gas was observed if acid is added too quickly. Once 50% of the acid is added, remaining acid can be added more quickly. After the solution stirred for an additional hour at 0 °C, a brown precipitate formed. The precipitate was filtered, washed with water, and dried under high vacuum, yielding a brown powder. Attempts to recrystallize this powder from water, or water/methanol solutions resulted in decomposition, therefore the crude **112** was carried forward without purification. IR (solid) 3518 (w), 3138 (br m), 2770 (br m), 1695 (w), 1646 (m), 1597 (m), 1536 (m), 1385 (s), 1046 (s), 927 (s), 878 (s), 792 (s); ^1H NMR (acetone- d_6) δ 2.29 (s, 3H), 6.55 (s, 1H); ^{13}C NMR (acetone- d_6) δ 19.0, 127.8, 146.9, 147.2, 155.8, 178.3, 184.0.

2,4-Dinitroorcinol **113**



A solution of crude dinitrosoorcinol **112** (35 mmol) in 80 mL of trifluoroacetic acid was cooled to 0 °C, and 12 mL (~117 mmol) of 30% aqueous hydrogen peroxide was added dropwise. After 4h of stirring, the solution was carefully concentrated *in vacuo* to remove most of the trifluoroacetic acid, then was washed with water, extracted with ethyl acetate, dried with MgSO₄, and concentrated *in vacuo*. Recrystallization from chloroform yielded 3.64 g (49% from orcinol) of **113** as yellow crystals (X-ray crystallographic analysis data included in Appendix), mp 159.0-160.0 °C. IR (solid) 3229 (m), 1635 (m), 1580 (s), 1519 (s), 1359 (s), 1304 (s), 1164 (s), 850 (m); ¹H NMR (Acetone-*d*₆) δ 2.43 (s, 3H), 6.68 (s, 1H), 10.93 (br s, 1H), 11.14 (br s, 1H); ¹³C NMR (Acetone-*d*₆) δ 19.9, 111.8, 126.5, 133.4, 141.6, 149.4, 156.0. Anal. calcd for C₇H₆N₂O₆: C, 39.26; H, 2.82; N, 13.08, found: C, 39.37; H, 2.81; N, 13.14.

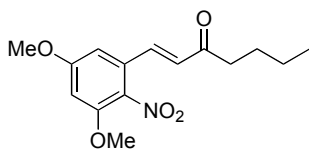
3,5-Dimethoxy-2,4-dinitrotoluene **115**



A solution of 776 mg (3.62 mmol) of dinitroorcinol **113**, 1.83 g (13.2 mmol) of potassium carbonate in 30 mL acetone was stirred at room temperature, then 1.03 mL (10.9 mmol) of dimethyl sulfate was added. The reaction mixture was heated to reflux for 4h. After cooling to room temperature, and concentration *in vacuo*, the crude residue was dissolved in diethyl ether, washed with 2M aqueous KOH, dried

with MgSO₄, and concentrated *in vacuo*. Recrystallization from hexanes yielded 800 mg (91%) of **115** as off-white needles, mp 92.0-92.5 °C, IR (thin film, NaCl) 3101 (w), 2988 (w), 2953 (m), 2860 (m), 1600 (s), 1536 (s), 1468 (s), 1361 (s), 1336 (s), 1225 (s), 1121 (s), 922 (m), 830 (m), 666 (s); ¹H NMR (CDCl₃) δ 2.39 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.65 (s, 1H); ¹³C NMR (CDCl₃) δ 18.6, 57.1, 64.4, 109.3, 134.5, 135.2, 139.5, 145.9, 152.5. Anal. calcd for C₉H₁₀N₂O₆: C, 44.63; H, 4.16; N, 11.57, found: C, 44.82; H, 4.23; N, 11.48.

(E)-1-(3,5-Dimethoxy-2-nitrophenyl)hept-1-en-3-one 118



A solution of 200 mg (0.682 mmol) of **105**, 34 mg (0.068 mmol) of tetrabutylammonium perrhenate, and 13 mg (0.068 mmol) of p-toluenesulfonic acid monohydrate in 5 mL CH₂Cl₂ was stirred at room temperature for 16h. The crude mixture was dissolved in diethyl ether, washed with saturated aqueous NaHCO₃, dried with MgSO₄, and concentrated *in vacuo*, yielding 182 mg (91%) of **118** as a yellow solid. IR (thin film, NaCl) 3103 (w), 2958 (s), 2937 (s), 2873 (m), 1696 (m), 1667 (m), 1592 (s), 1526 (s), 1342 (s), 1207 (s), 1170 (s), 1089 (m), 969 (m), 840 (m); ¹H NMR (CDCl₃) δ 0.91 (t, 3H, *J* = 7 Hz), 1.35 (m, 2H), 1.61 (m, 2H), 2.63 (t, 2H, *J* = 7 Hz), 3.85 (s, 3H), 3.87 (s, 3H), 6.55 (d, 1H, *J* = 2 Hz), 6.61-6.65 (m, 2H), 7.37 (d, 1H, *J* = 16 Hz); ¹³C NMR (CDCl₃) δ 14.0, 22.4, 26.2, 40.2, 56.0, 56.7, 101.0, 102.5, 130.2, 131.3, 135.0, 135.4, 153.1, 161.7, 200.1.

Appendix

X-ray Crystallographic Data for 3,5-Dinitroorcinol 113.....	133
^1H and ^{13}C NMR Spectra from Select Synthetic Products.....	141

Crystal Structure Information for **UM # 1575**

Issued by: Peter Y. Zavalij

Crystal No. & ID : **1575**: DeShong/Sandelier MJS-I-85Y
Compound name : Organic compound
Chemical formula : $C_7H_6N_2O_6$
Final R_1 [$I > 2\sigma(I)$] : **3.70 %**

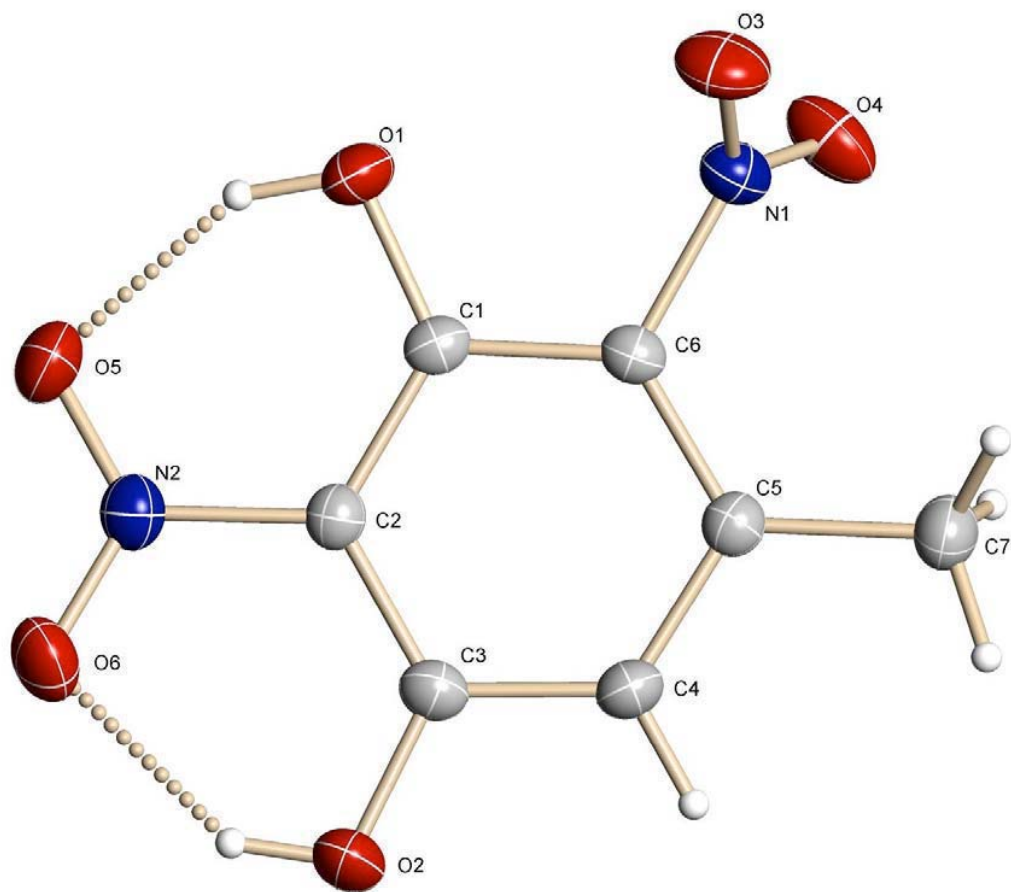


Figure 1. A view of UM#1575 showing the numbering scheme employed. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 30% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

A yellow prism of $C_7H_6N_2O_6$, approximate dimensions $0.11 \times 0.21 \times 0.26 \text{ mm}^3$, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 298(2) K on a three-circle diffractometer system equipped with Bruker Smart1000 CCD area detector using a graphite monochromator and a $MoK\alpha$ fine-focus sealed tube ($\lambda = 0.71073 \text{ \AA}$). The detector was placed at a distance of 4.939 cm from the crystal.

A total of 3024 frames were collected with a scan width of 0.3° an exposure time of 23 sec/frame using SMART (Bruker, 1999). The total data collection time was 25.3 hours. The frames were integrated with SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 8148 reflections to a maximum θ angle of 27.50° , of which 1954 were independent (completeness = 99.6%, $R_{\text{int}} = 2.43\%$, $R_{\text{sig}} = 1.67\%$) and 1568 were greater than $2\sigma(I)$. The final cell dimensions of $a = 7.157(2) \text{ \AA}$, $b = 12.348(4) \text{ \AA}$, $c = 10.056(3) \text{ \AA}$, $\alpha = 90^\circ$, $\beta = 105.800(5)^\circ$, $\gamma = 90^\circ$, $V = 855.1(4) \text{ \AA}^3$, are based upon the refinement of the XYZ-centroids of 3466 reflections with $2.7 < \theta < 29.0^\circ$ using SAINT software. Analysis of the data showed 0 % decay during data collection. Data were corrected for absorption effects with the Semi-empirical from equivalents method using SADABS (Sheldrick, 1996). The minimum and maximum transmission coefficients were 0.915 and 0.984.

The structure was solved and refined using the SHELXS-97 (Sheldrick, 1990) and SHELXL-97 (Sheldrick, 1997) software in the space group $P2_1/n$ with $Z = 4$ for the formula unit $C_7H_6N_2O_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 156 variables converged at $R_1 = 3.70\%$ for the observed data and $wR_2 = 7.46\%$ for all data. The goodness-of-fit was 1.000. The largest peak on the final difference map was 0.202 e/\AA^3 and the largest hole was -0.164 e/\AA^3 . On the basis of the final model, the calculated density was 1.663 g/cm^3 and $F(000)$, 440 e .

Overall structure quality considerations:

1. Strong data set, no disorder, R_1 4% maximum. Publishable quality.
 2. Good data set, perhaps some minor disorder, R_1 6% maximum. Publishable quality.
 3. Average data set and/or easily modeled disorder or twinning. Publishable with care.
 4. Weak data and/or major disorder or twinning that is not easily modeled. Publishable in some cases.
 5. Very weak data and/or unexplained features of data or model. Not of publishable quality.
- A structure with a quality factor of 4 or 5 should not be used for a regulatory document without prior consultation.

Comments:

- Data quality: very good
- Twinning: none
- Disorder: moderate - CH_3 and 1 of 2 NO_2 group show rotation disorder; the former in about 3:2 ratio and the latter in about 10:1 ratio
- H-atoms: constrained geometry as riding on attached atom (A) except H atoms of hydroxyl groups which were refined freely; Uiso refined
- Residual density: in the middle of the bonds
- Structure quality: very good
- Publishable Yes

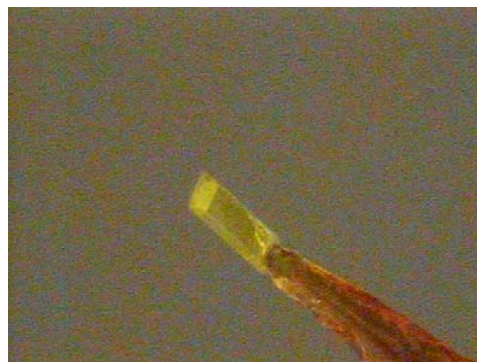
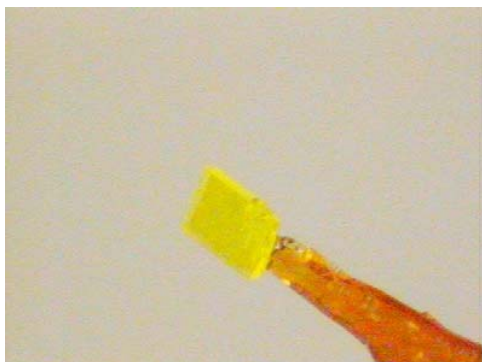


Table 1. Crystal data and structure refinement for UM#1575.

X-ray lab book No.	1575
Crystal ID	DeShong/Sandelier MJS-I-85Y
Empirical formula	C ₇ H ₆ N ₂ O ₆
Formula weight	214.14
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal size	0.26×0.21×0.11 mm ³
Crystal habit	yellow prism
Crystal system	monoclinic
Space group	<i>P</i> 2 ₁ / <i>n</i>
Unit cell dimensions	<i>a</i> = 7.157(2) Å α = 90° <i>b</i> = 12.348(4) Å β = 105.800(5)° <i>c</i> = 10.056(3) Å γ = 90°
Volume	855.1(4) Å ³
Z	4
Density, ρ_{calc}	1.663 g/cm ³
Absorption coefficient, μ	0.149 mm ⁻¹
F(000)	440e ⁻
Diffractometer	Bruker Smart1000 CCD area detector
Radiation source	fine-focus sealed tube, MoK α
Detector distance	4.939 cm
Data collection method	ω and scans
Total frames	3024
Frame size	512 pixels
Frame width	0.3°
Exposure per frame	23 sec
Total measurement time	25.3 hours
θ range for data collection	3.13 to 27.50°
Index ranges	-9 ≤ <i>h</i> ≤ 9, -16 ≤ <i>k</i> ≤ 15, -12 ≤ <i>l</i> ≤ 13
Reflections collected	8148
Independent reflections	1954
Observed reflection, <i>I</i> > 2 σ (<i>I</i>)	1568
Coverage of independent reflections	99.6 %
Variation in check reflections	0 %
Absorption correction	Semi-empirical from equivalents SADABS (Sheldrick, 1996)
Max. and min. transmission	0.984 and 0.915
Structure solution technique	direct
Structure solution program	SHELXS-97 (Sheldrick, 1990)
Refinement technique	Full-matrix least-squares on F ²
Refinement program	SHELXL-97 (Sheldrick, 1997)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	1954 / 3 / 156
Goodness-of-fit on F ²	1.000
$\Delta/\sigma_{\text{max}}$	0.000
Final R indices:	
R ₁ , <i>I</i> > 2 σ (<i>I</i>)	0.0370
wR ₂ , all data	0.0746
R _{int}	0.0243
R _{sig}	0.0167
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.01P)^2 + 0.393P]$, $P = [\max(F_o^2, 0) + 2F_o^2]/3$
Extinction coefficient	0.0227(13)
Largest diff. peak and hole	0.202 and -0.164 e ⁻ /Å ³

$$R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|, \quad wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^3]^{1/2}$$

Table 2. Atomic coordinates and equivalent* isotropic atomic displacement parameters (\AA^2) for UM#1575.

Atom	x/a	y/b	z/c	U_{eq}
O1	0.34608(14)	0.10075(9)	0.66217(11)	0.0539(3)
O2	1.02283(15)	-0.00639(10)	0.75387(12)	0.0619(3)
N1	0.38064(16)	0.23084(9)	0.45880(12)	0.0473(3)
O3	0.3246(2)	0.30416(12)	0.51937(18)	0.0701(5)
O4	0.3066(3)	0.20886(13)	0.33733(15)	0.0728(5)
N1A	0.38064(16)	0.23084(9)	0.45880(12)	0.0473(3)
O3A	0.373(3)	0.3237(9)	0.494(2)	0.0701(5)
O4A	0.249(2)	0.1850(12)	0.3763(17)	0.0728(5)
N2	0.66373(18)	-0.02168(10)	0.83297(12)	0.0500(3)
O5	0.50146(17)	-0.03530(10)	0.85109(12)	0.0693(3)
O6	0.81017(17)	-0.06278(10)	0.91123(11)	0.0673(3)
C1	0.52287(17)	0.10239(10)	0.64144(13)	0.0386(3)
C2	0.68367(18)	0.04275(10)	0.71925(12)	0.0398(3)
C3	0.86199(18)	0.04758(11)	0.68548(14)	0.0439(3)
C4	0.87566(19)	0.11050(11)	0.57492(14)	0.0463(3)
C5	0.72180(18)	0.17067(10)	0.49729(13)	0.0419(3)
C6	0.54841(17)	0.16611(10)	0.53433(13)	0.0391(3)
C7	0.7471(2)	0.23866(13)	0.37993(15)	0.0556(4)

* U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2a. Site occupancy factors that deviate from unity for UM#1575.

Atom	sof	Atom	sof	Atom	sof
N1	0.910(4)	O3	0.910(4)	O4	0.910(4)
N1A	0.090(4)	O3A	0.090(4)	O4A	0.090(4)
H7A	0.632(15)	H7B	0.632(15)	H7C	0.632(15)
H7D	0.368(15)	H7E	0.368(15)	H7F	0.368(15)

Table 3. Anisotropic atomic displacement parameters* (\AA^2) for UM#1575.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	0.0421(5)	0.0609(6)	0.0643(6)	0.0031(5)	0.0237(5)	0.0015(5)
O2	0.0434(5)	0.0732(7)	0.0659(7)	0.0199(6)	0.0094(5)	0.0107(5)
N1	0.0434(6)	0.0420(6)	0.0536(7)	0.0000(5)	0.0084(5)	0.0026(5)
O3	0.0647(10)	0.0643(8)	0.0798(10)	-0.0116(7)	0.0169(7)	0.0231(7)
O4	0.0831(10)	0.0641(9)	0.0537(8)	-0.0025(7)	-0.0115(7)	0.0168(7)
N1A	0.0434(6)	0.0420(6)	0.0536(7)	0.0000(5)	0.0084(5)	0.0026(5)
O3A	0.0647(10)	0.0643(8)	0.0798(10)	-0.0116(7)	0.0169(7)	0.0231(7)
O4A	0.0831(10)	0.0641(9)	0.0537(8)	-0.0025(7)	-0.0115(7)	0.0168(7)
N2	0.0575(7)	0.0499(7)	0.0424(6)	-0.0001(5)	0.0134(5)	-0.0045(6)
O5	0.0689(7)	0.0812(8)	0.0668(7)	0.0144(6)	0.0338(6)	-0.0055(6)
O6	0.0712(7)	0.0726(7)	0.0516(6)	0.0181(5)	0.0055(5)	0.0024(6)
C1	0.0360(6)	0.0388(6)	0.0419(6)	-0.0078(5)	0.0123(5)	-0.0027(5)
C2	0.0435(6)	0.0393(6)	0.0366(6)	-0.0016(5)	0.0112(5)	-0.0033(5)
C3	0.0377(6)	0.0451(7)	0.0458(7)	-0.0010(6)	0.0063(5)	0.0018(5)
C4	0.0369(6)	0.0530(8)	0.0513(7)	0.0021(6)	0.0161(6)	0.0006(6)
C5	0.0437(7)	0.0412(7)	0.0417(7)	-0.0018(5)	0.0130(5)	-0.0014(5)
C6	0.0373(6)	0.0378(6)	0.0404(6)	-0.0024(5)	0.0072(5)	0.0021(5)
C7	0.0617(9)	0.0554(9)	0.0543(8)	0.0085(7)	0.0236(7)	0.0007(7)

* The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2hka^*b^*U_{12}]$

Table 4. Hydrogen atom coordinates and isotropic atomic displacement parameters (\AA^2) for UM#1575.

Atom	x/a	y/b	z/c	U_{iso}
H1	0.354(3)	0.0546(16)	0.727(2)	0.085(6)
H2	0.997(3)	-0.0413(16)	0.819(2)	0.089(7)
H4	0.9930	0.1124	0.5519	0.051(4)
H7A	0.8828	0.2442	0.3853	0.056(4)
H7B	0.6952	0.3097	0.3855	0.056(4)
H7C	0.6797	0.2056	0.2938	0.056(4)
H7D	0.6223	0.2621	0.3245	0.056(4)
H7E	0.8099	0.1967	0.3242	0.056(4)
H7F	0.8254	0.3007	0.4159	0.056(4)

Table 5. Bond lengths (Å), valence and torsion angles (°) for UM#1575.

O1-C1	1.3373(15)	O1-H1	0.859(19)	O2-C3	1.3457(16)
O2-H2	0.84(2)	N1-O3	1.2185(16)	N1-O4	1.2222(16)
N1-C6	1.4700(16)	N2-O5	1.2351(16)	N2-O6	1.2354(15)
N2-C2	1.4318(17)	C1-C6	1.3855(18)	C1-C2	1.4102(17)
C2-C3	1.4084(18)	C3-C4	1.3815(19)	C4-C5	1.3805(18)
C5-C6	1.3906(18)	C5-C7	1.4989(19)		
C1-O1-H1	105.2(13)	C3-O2-H2	108.1(13)	O3-N1-O4	123.53(14)
O3-N1-C6	118.66(13)	O4-N1-C6	117.80(12)	O5-N2-O6	121.26(12)
O5-N2-C2	119.72(12)	O6-N2-C2	119.03(12)	O1-C1-C6	117.42(11)
O1-C1-C2	124.72(12)	C6-C1-C2	117.86(11)	C3-C2-C1	120.03(12)
C3-C2-N2	120.66(11)	C1-C2-N2	119.31(11)	O2-C3-C4	116.84(12)
O2-C3-C2	124.13(13)	C4-C3-C2	119.02(12)	C5-C4-C3	122.50(12)
C4-C5-C6	117.35(12)	C4-C5-C7	119.85(12)	C6-C5-C7	122.80(12)
C1-C6-C5	123.20(11)	C1-C6-N1	116.64(11)	C5-C6-N1	120.17(11)
O1-C1-C2-C3	177.80(12)	C6-C1-C2-C3	-1.15(18)	O1-C1-C2-N2	-2.68(19)
C6-C1-C2-N2	178.36(11)	O5-N2-C2-C3	-171.41(13)	O6-N2-C2-C3	8.50(19)
O5-N2-C2-C1	9.07(19)	O6-N2-C2-C1	-171.01(12)	C1-C2-C3-O2	179.94(12)
N2-C2-C3-O2	0.4(2)	C1-C2-C3-C4	-0.58(19)	N2-C2-C3-C4	179.91(12)
O2-C3-C4-C5	-179.30(13)	C2-C3-C4-C5	1.2(2)	C3-C4-C5-C6	0.0(2)
C3-C4-C5-C7	179.05(13)	O1-C1-C6-C5	-176.60(12)	C2-C1-C6-C5	2.44(19)
O1-C1-C6-N1	3.44(17)	C2-C1-C6-N1	-177.52(11)	C4-C5-C6-C1	-1.88(19)
C7-C5-C6-C1	179.10(13)	C4-C5-C6-N1	178.09(12)	C7-C5-C6-N1	-0.93(19)
O3-N1-C6-C1	66.49(18)	O4-N1-C6-C1	-114.57(17)	O3-N1-C6-C5	-113.47(17)
O4-N1-C6-C5	65.47(19)				

Table 7. Hydrogen bond information for UM#1575 (Å and °).

D—H...A*	d(D—H)	d(H...A)	d(D...A)	∠(DHA)
O1—H1...O5	0.859(19)	1.783(19)	2.5529(17)	148.0(18)
O1—H1...O2#1	0.859(19)	2.568(19)	3.0190(17)	113.8(15)
O2—H2...O6	0.84(2)	1.85(2)	2.5723(17)	143.7(19)
O2—H2...O3A#2	0.84(2)	2.50(2)	3.217(13)	144.1(18)
O2—H2...O3#2	0.84(2)	2.61(2)	3.242(2)	133.2(17)

* D - donor atom, H - hydrogen, A - acceptor.

Symmetry transformation codes: #1 x-1,y,z #2 -x+3/2,y-1/2,-z+3/2

Table 8. Least-squares planes (x,y,z in crystal coordinates) and angles between planes
(* indicates atom used to define plane)

- 0.2090 (0.0058) x + 10.0695 (0.0061) y + 5.6728 (0.0063) z = 4.3679 (0.0057)

* -0.0001 (0.0003) C2
 * 0.0004 (0.0010) N2
 * -0.0002 (0.0004) O5
 * -0.0001 (0.0004) O6

Rms deviation of fitted atoms = 0.0002

0.8625 (0.0038) x + 9.5630 (0.0049) y + 5.6790 (0.0046) z = 5.0831 (0.0029)

Angle to previous plane (with approximate esd) = 9.24 (0.09)

* -0.0103 (0.0008) C1
 * -0.0001 (0.0009) C2
 * 0.0081 (0.0009) C3
 * -0.0062 (0.0010) C4
 * -0.0043 (0.0009) C5
 * 0.0128 (0.0009) C6
 0.0012 (0.0023) C7
 -0.0607 (0.0018) O1
 0.0192 (0.0020) O2
 0.0582 (0.0019) N1_a
 0.0582 (0.0019) N1A_b
 0.0125 (0.0019) N2
 -0.1550 (0.0023) O5
 0.1901 (0.0022) O6

Rms deviation of fitted atoms = 0.0081

5.1574 (0.0045) x + 7.8642 (0.0123) y - 4.6247 (0.0145) z = 1.6620 (0.0086)

Angle to previous plane (with approximate esd) = 65.80 (0.08)

* 0.0015 (0.0003) C6
 * -0.0053 (0.0011) N1_a
 * 0.0019 (0.0004) O3_a
 * 0.0019 (0.0004) O4_a

Rms deviation of fitted atoms = 0.0031

- 4.7615 (0.0430) x - 3.0682 (0.1646) y + 8.6333 (0.0714) z = 1.4809 (0.0809)

Angle to previous plane (with approximate esd) = 33.84 (0.87)

* 0.0113 (0.0021) C6
* -0.0406 (0.0075) N1A_b
* 0.0146 (0.0027) O3A_b
* 0.0147 (0.0027) O4A_b

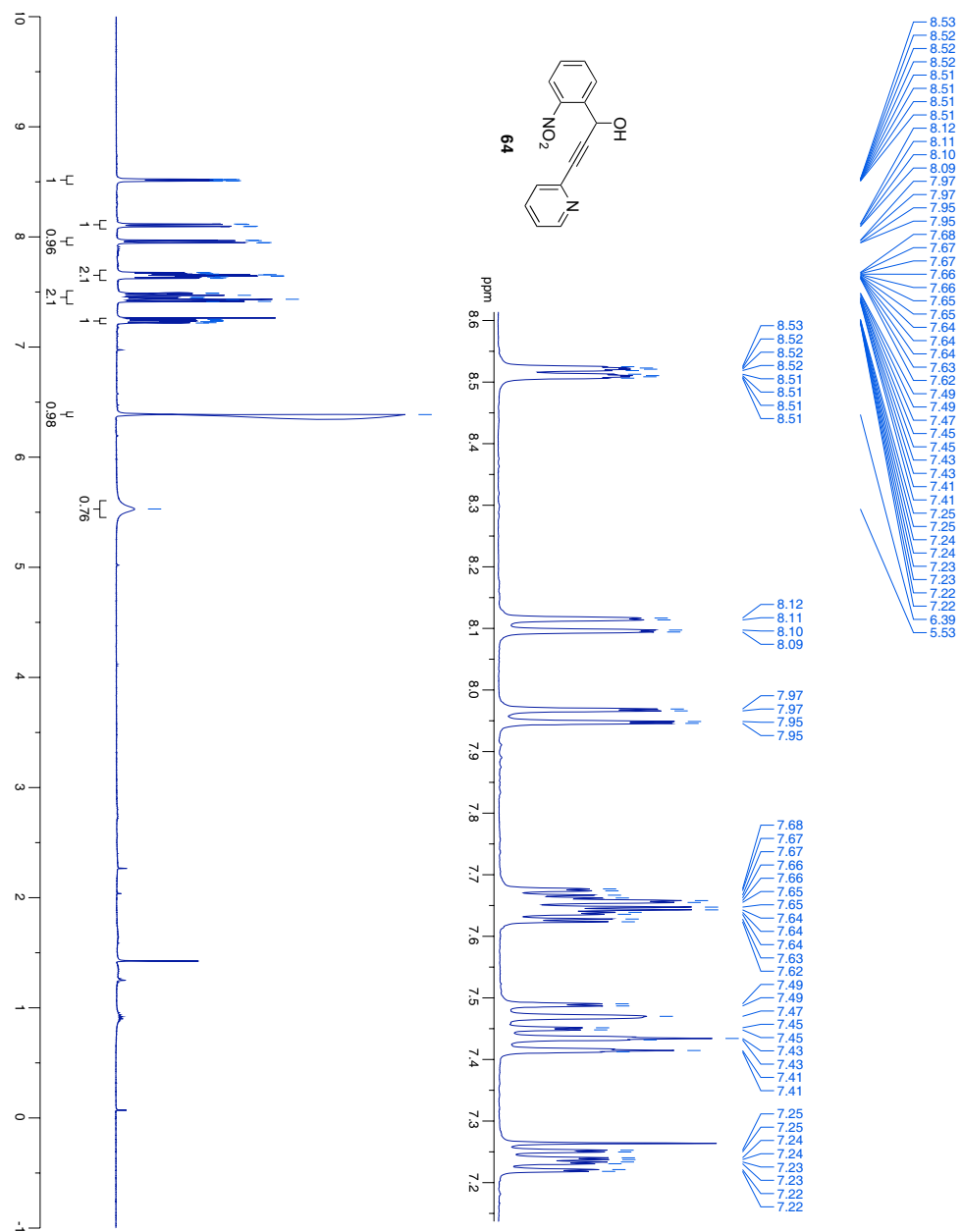
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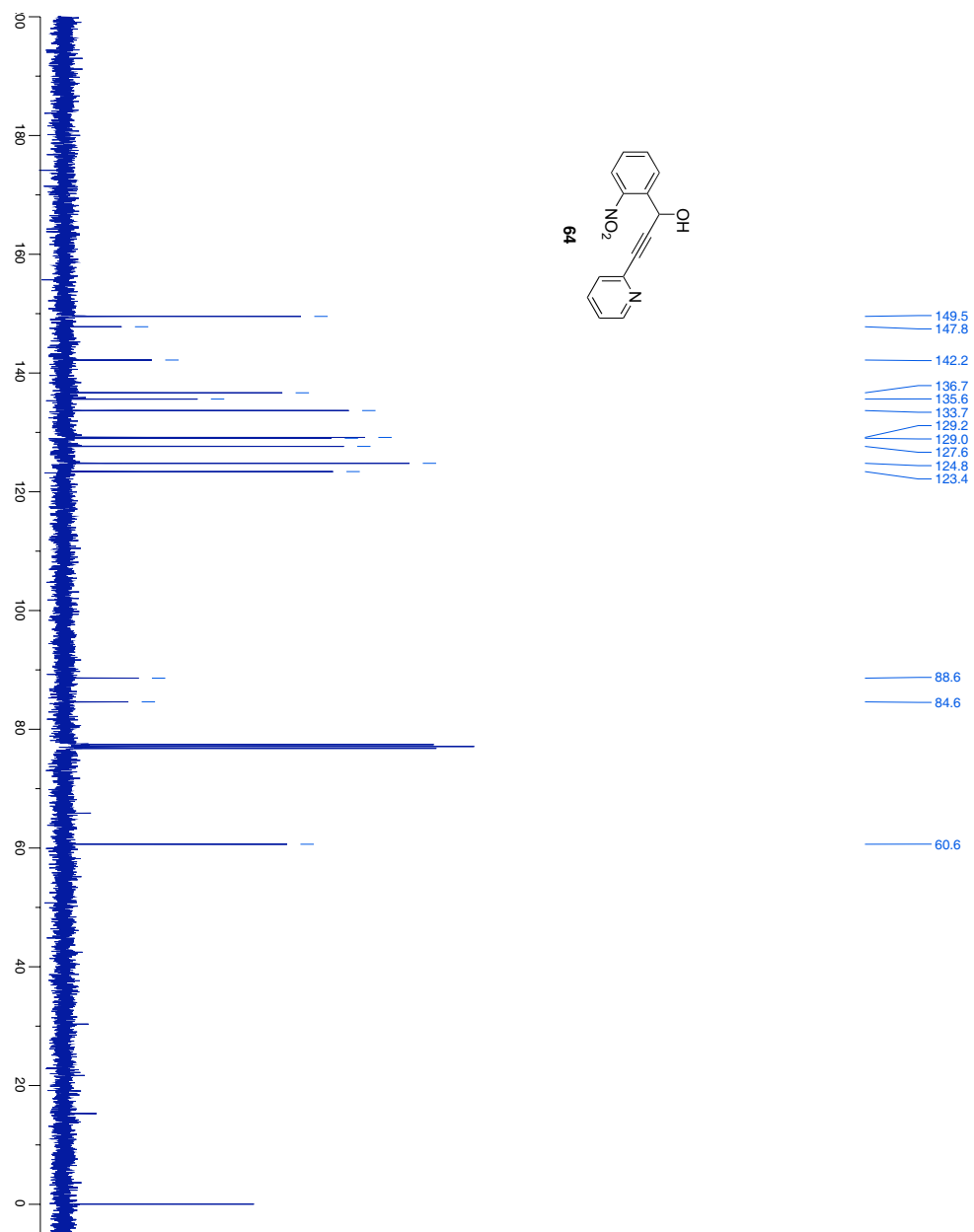
0.8625 (0.0038) x + 9.5630 (0.0049) y + 5.6790 (0.0046) z = 5.0831 (0.0029)

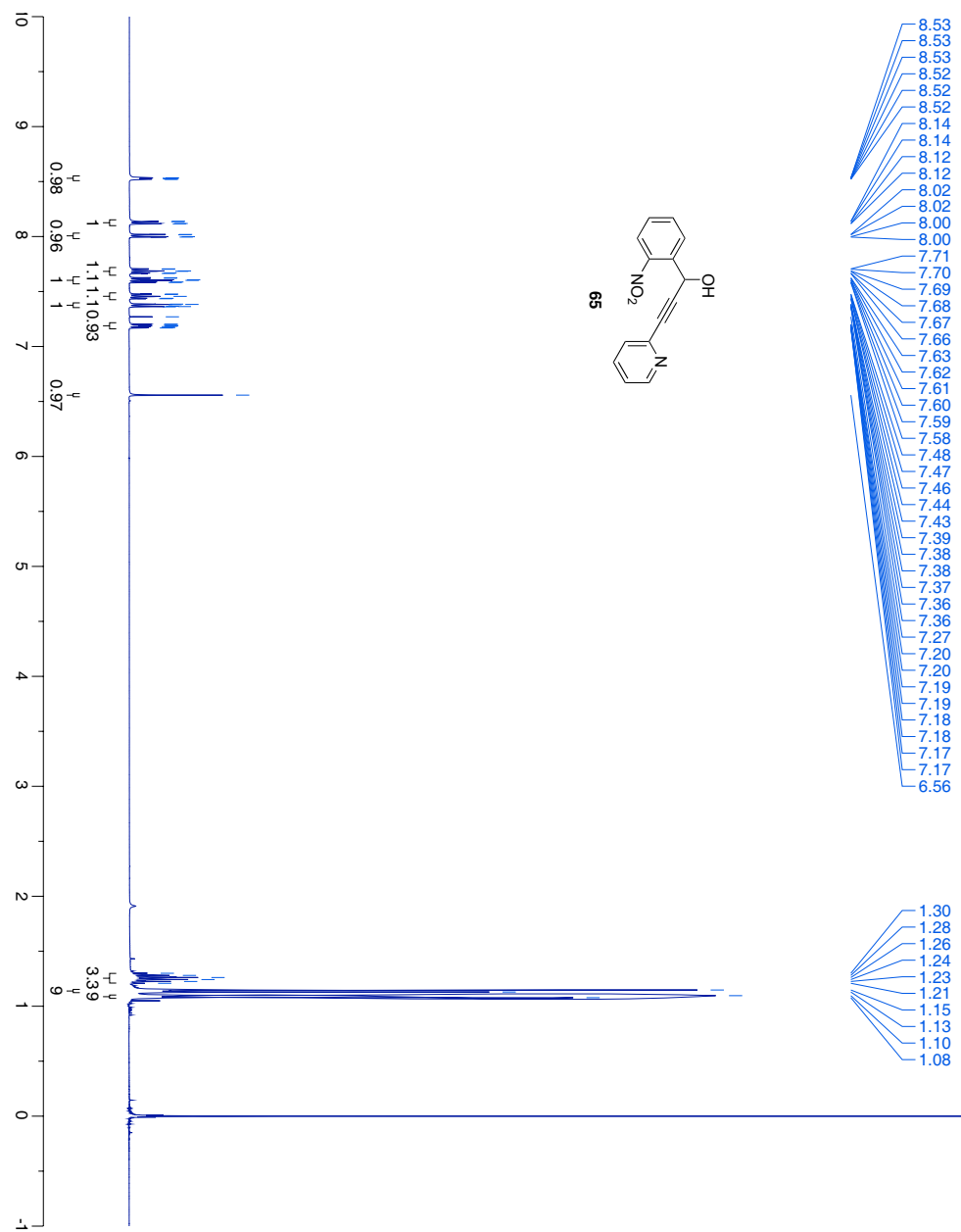
Angle to previous plane (with approximate esd) = 80.53 (0.66)

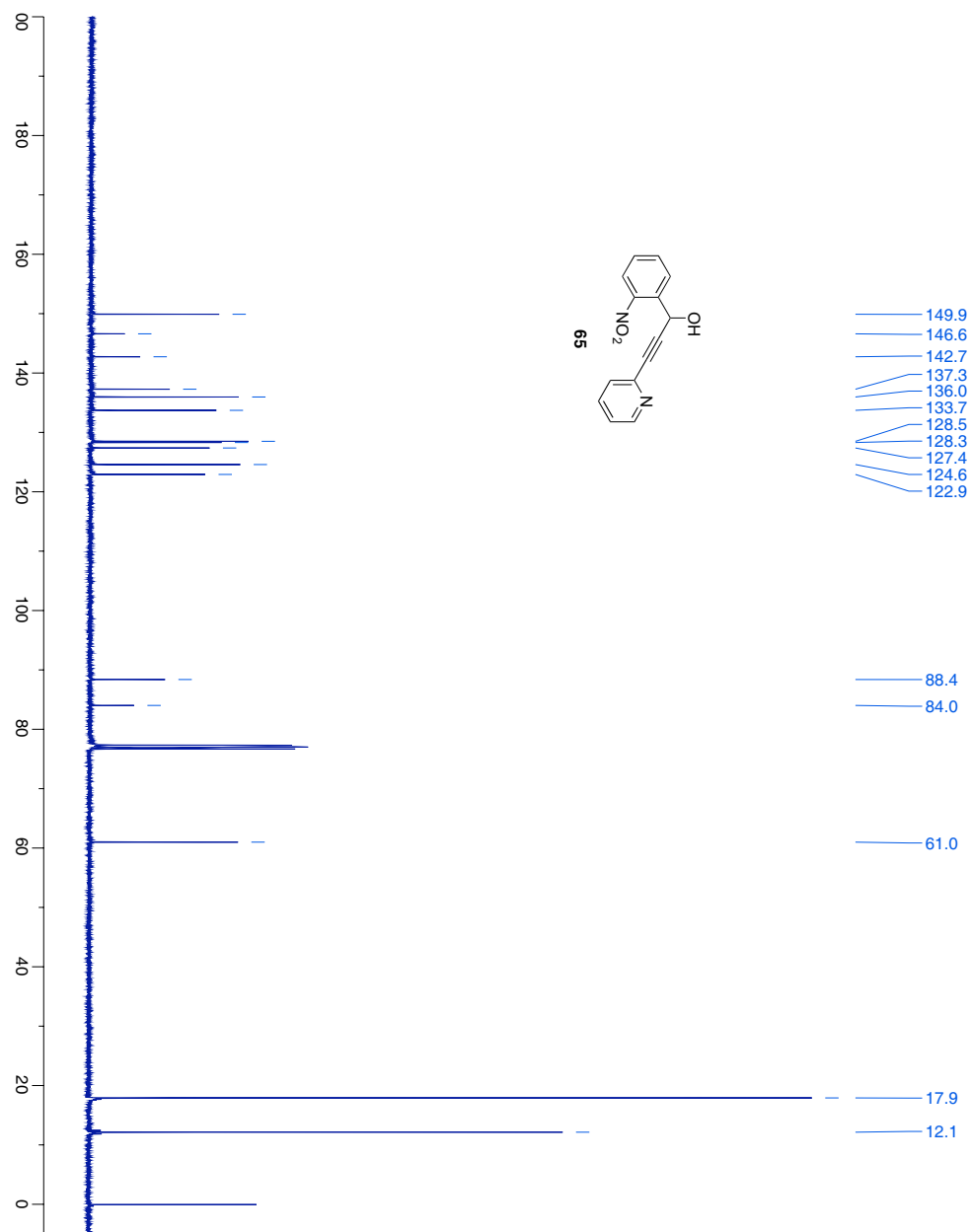
* -0.0103 (0.0008) C1
* -0.0001 (0.0009) C2
* 0.0081 (0.0009) C3
* -0.0062 (0.0010) C4
* -0.0043 (0.0009) C5
* 0.0128 (0.0009) C6
0.0012 (0.0023) C7
-0.0607 (0.0018) O1
0.0192 (0.0020) O2
0.0582 (0.0019) N1_a
1.0549 (0.0023) O3_a
-0.9057 (0.0023) O4_a
0.0582 (0.0019) N1A_b
1.1405 (0.0113) O3A_b
-0.9625 (0.0115) O4A_b
0.0125 (0.0019) N2
-0.1550 (0.0023) O5
0.1901 (0.0022) O6

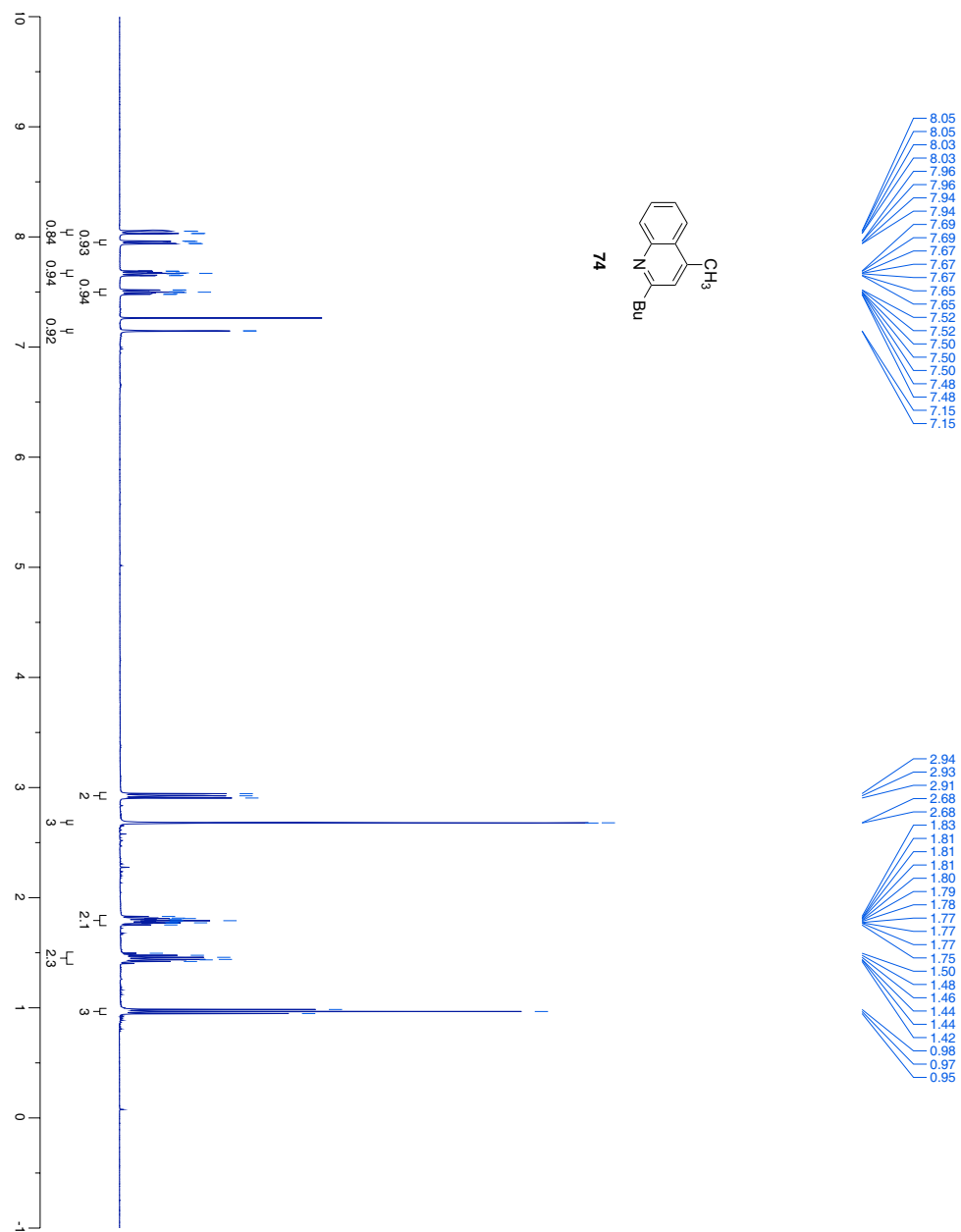
Rms deviation of fitted atoms = 0.0081

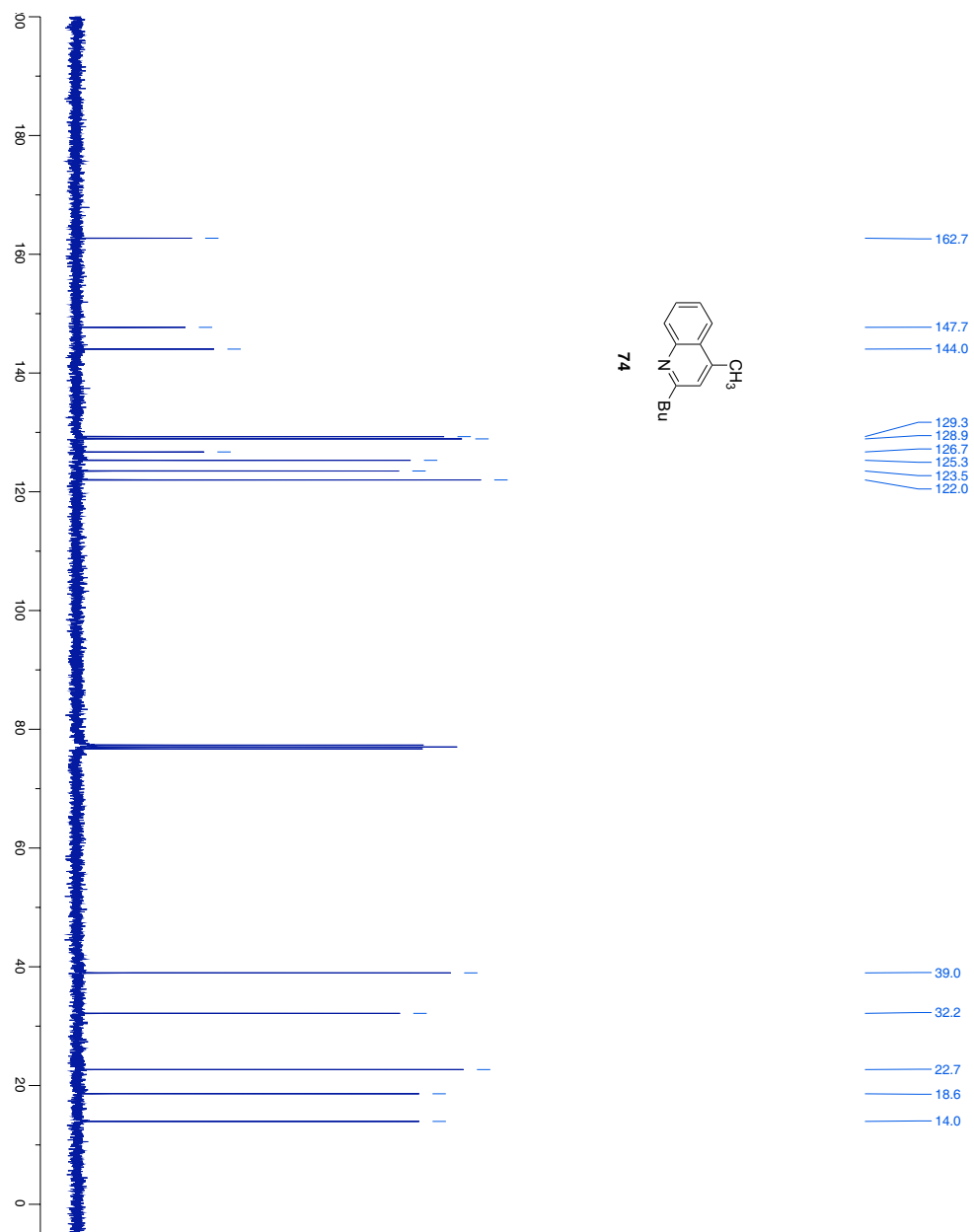


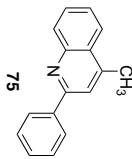


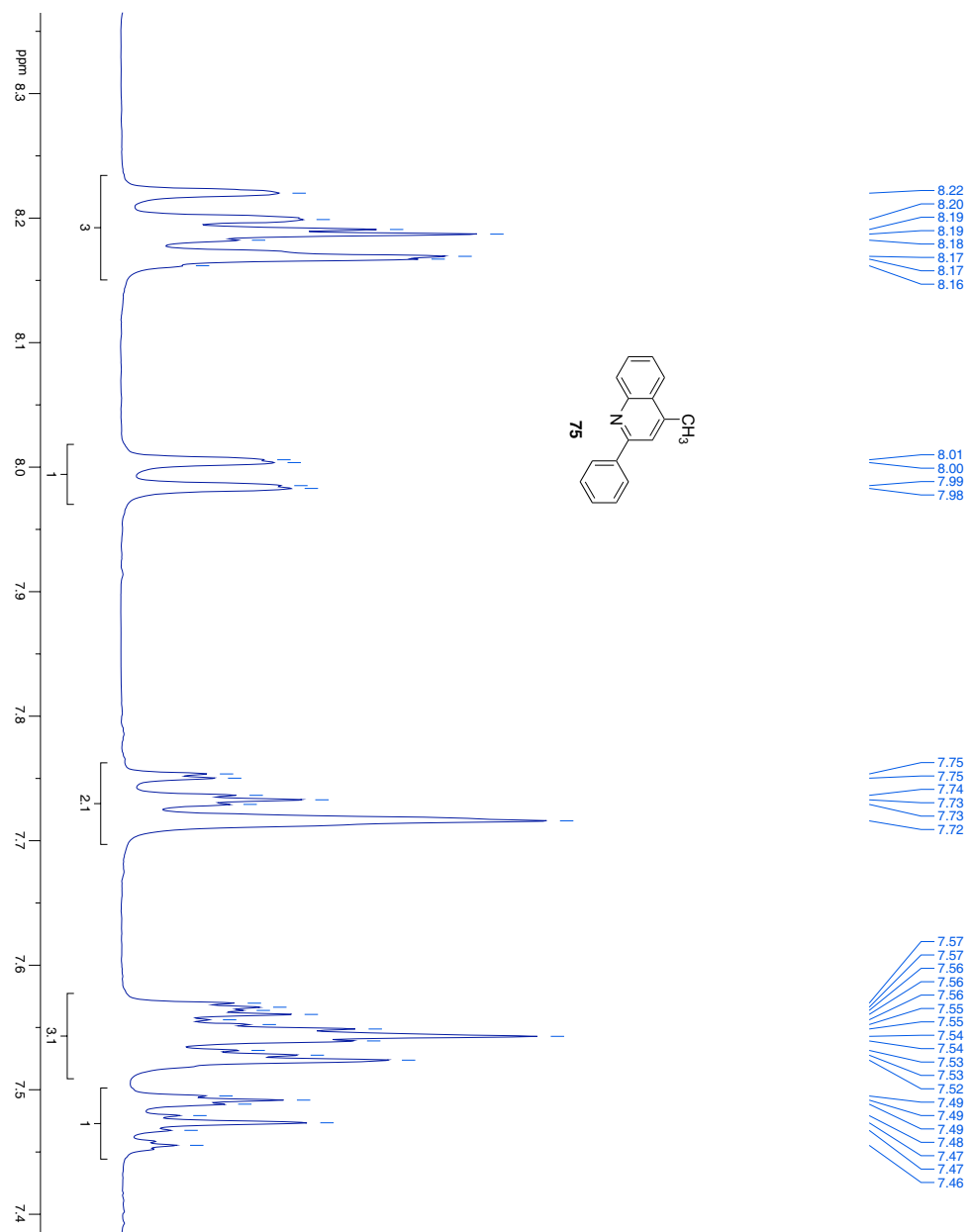


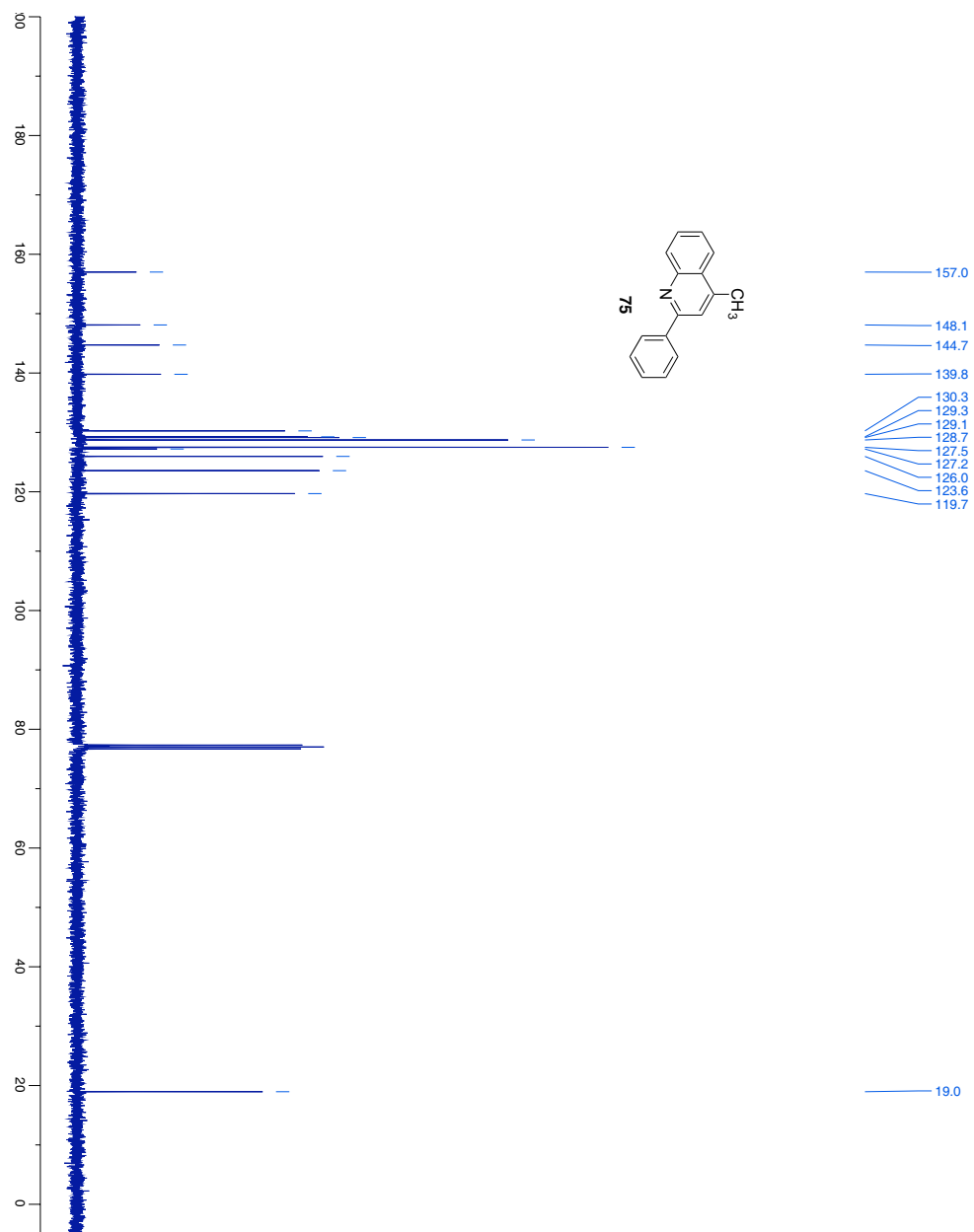


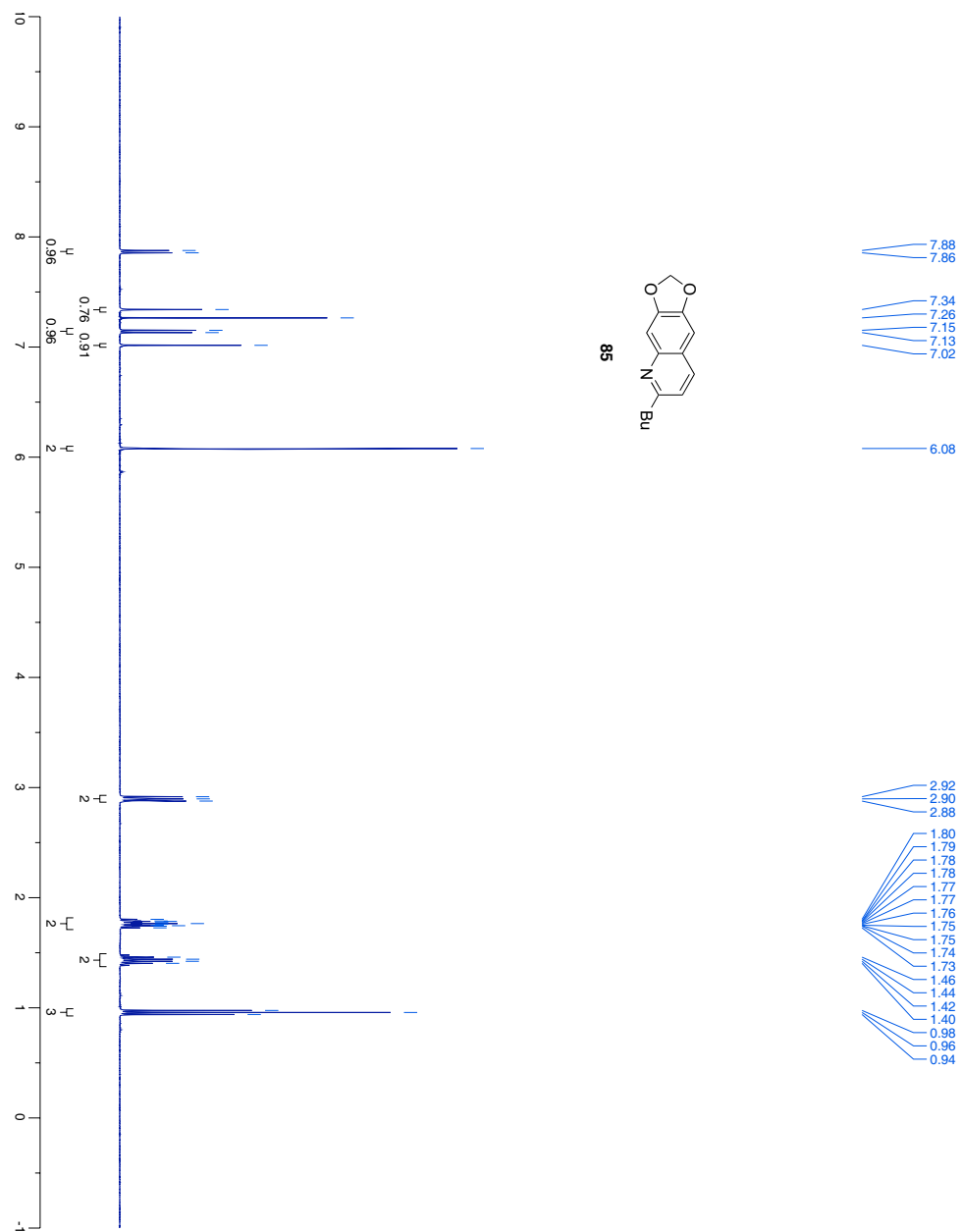


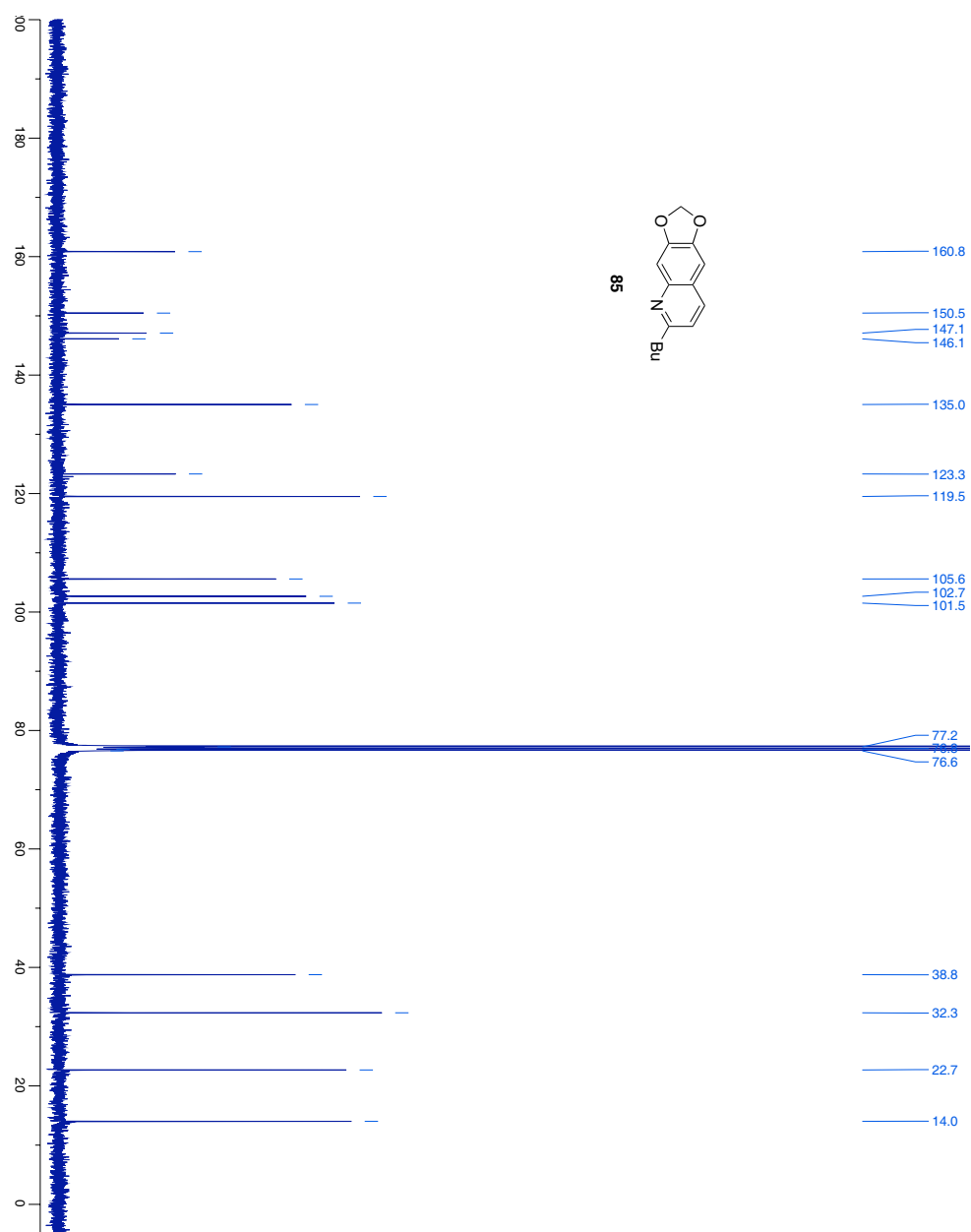




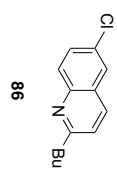




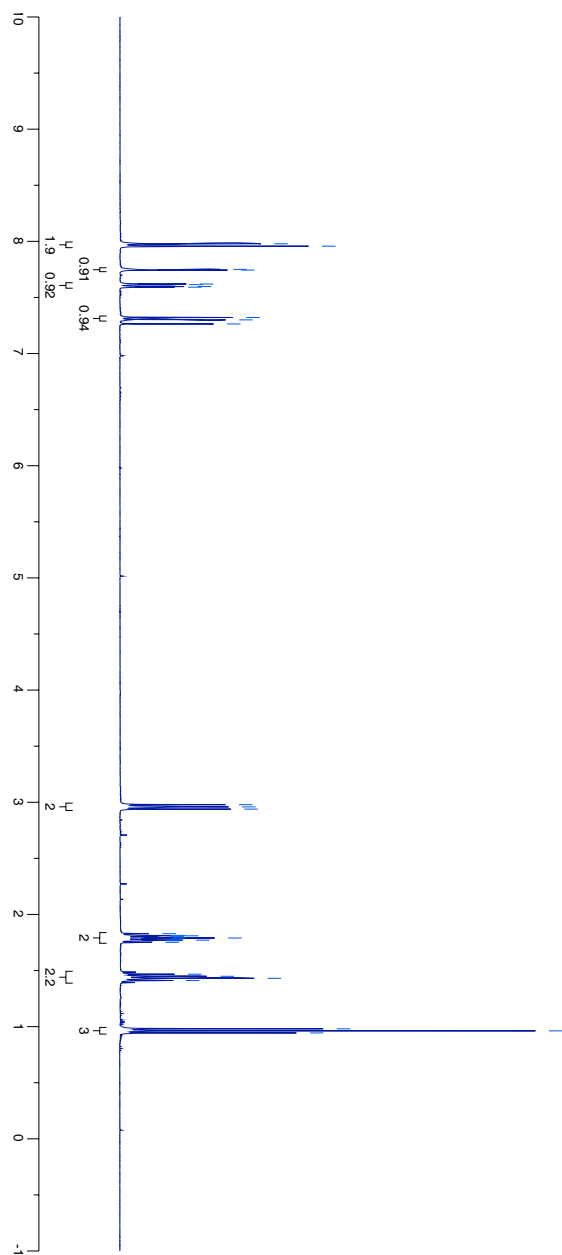


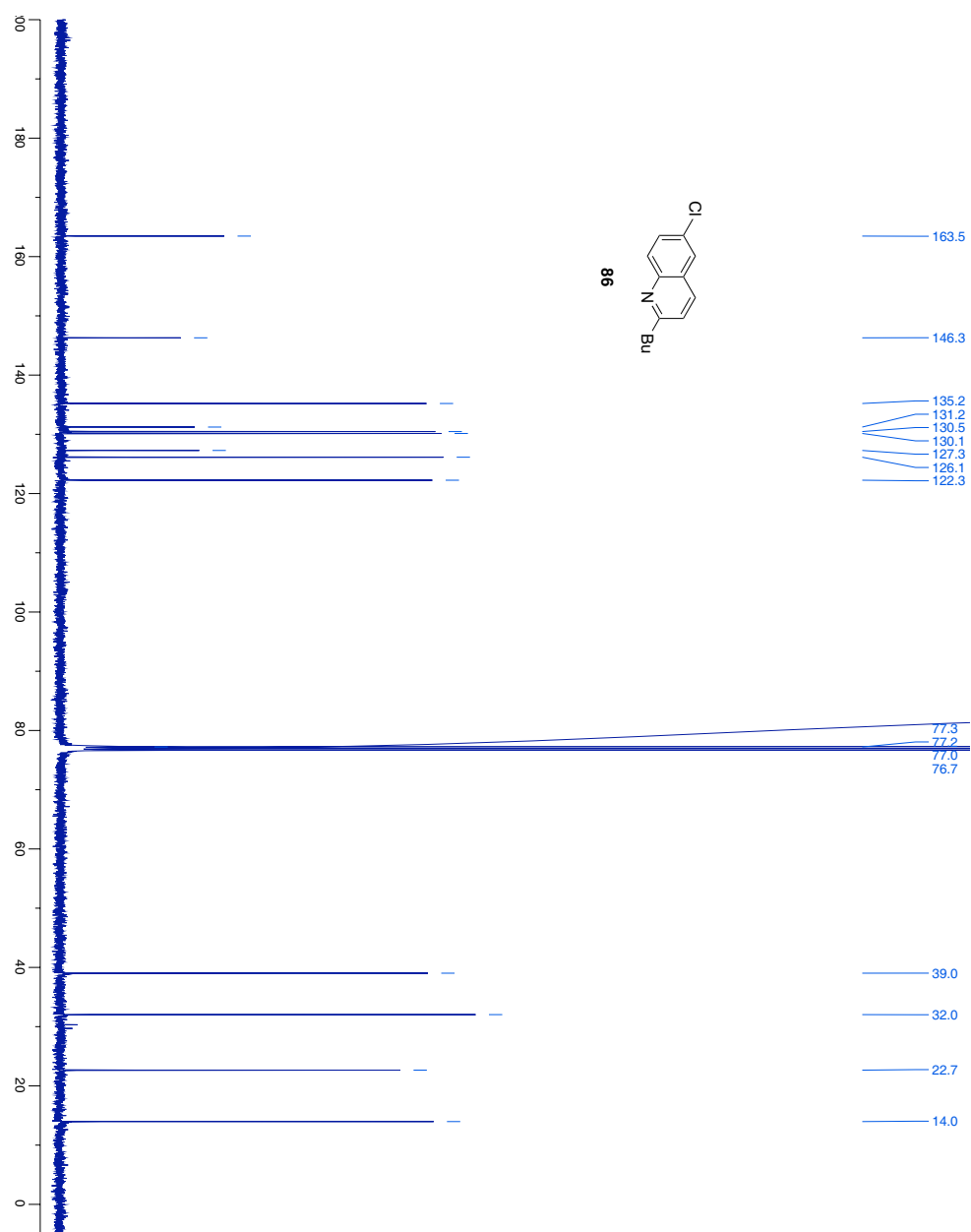


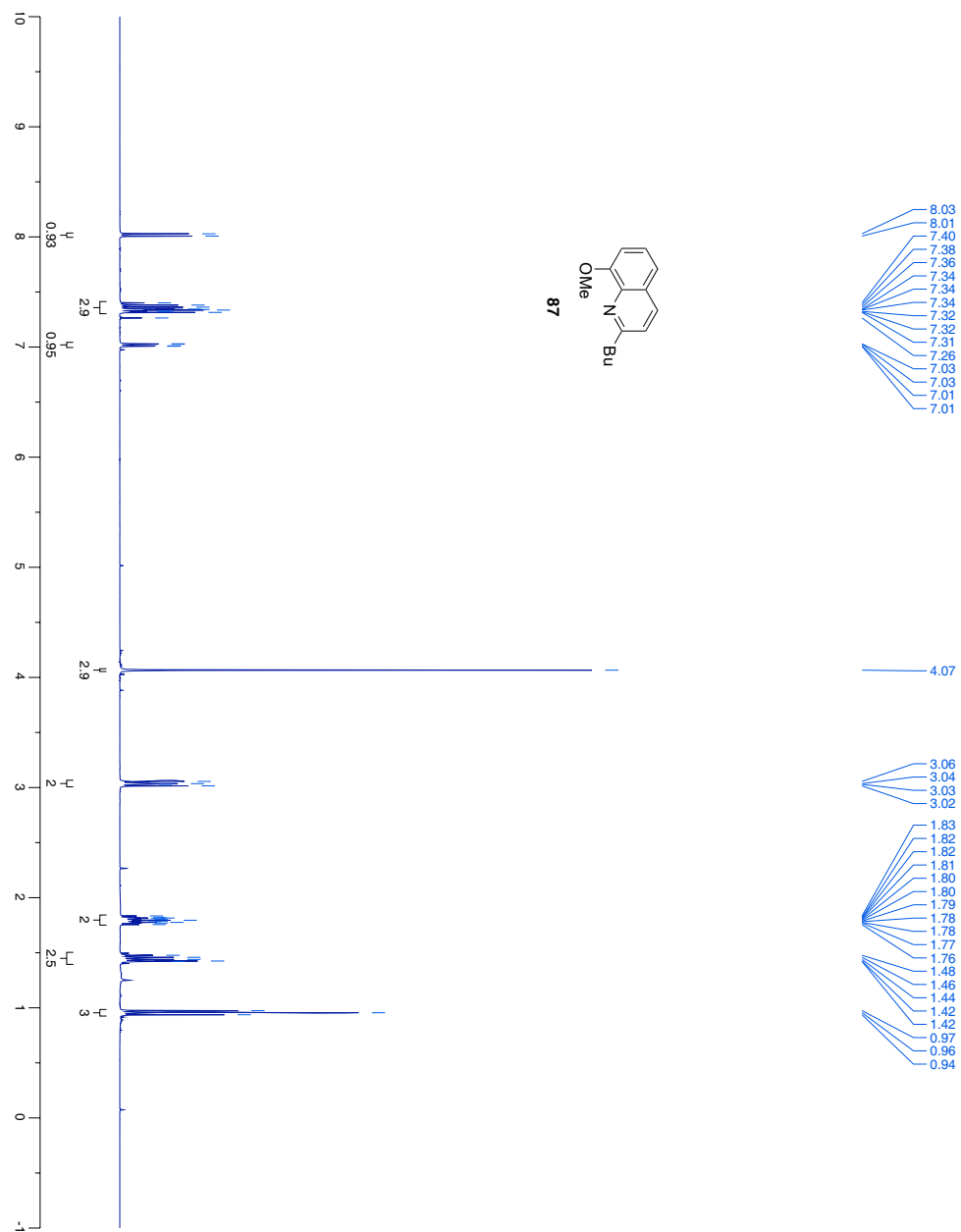
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7.30
7.26

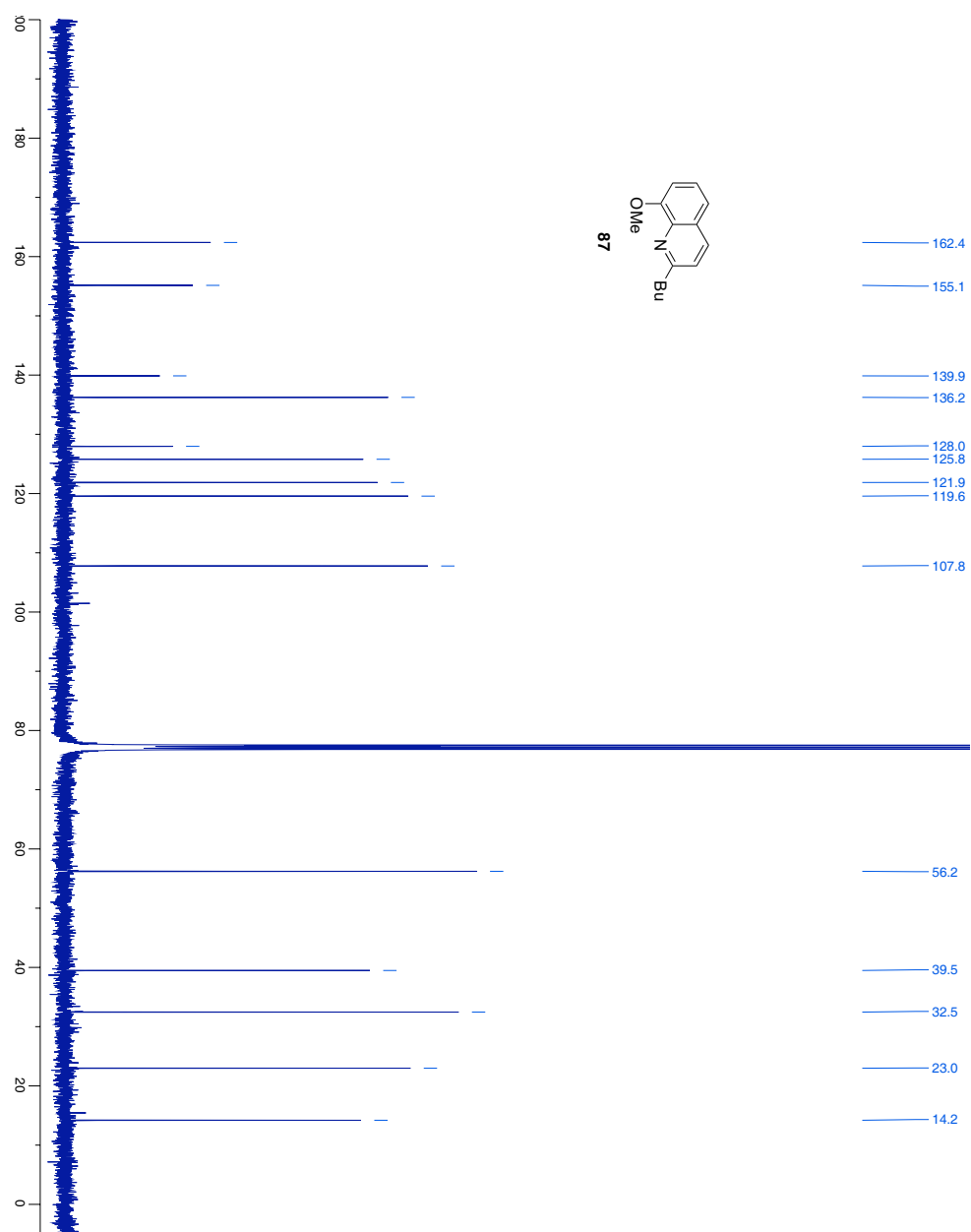


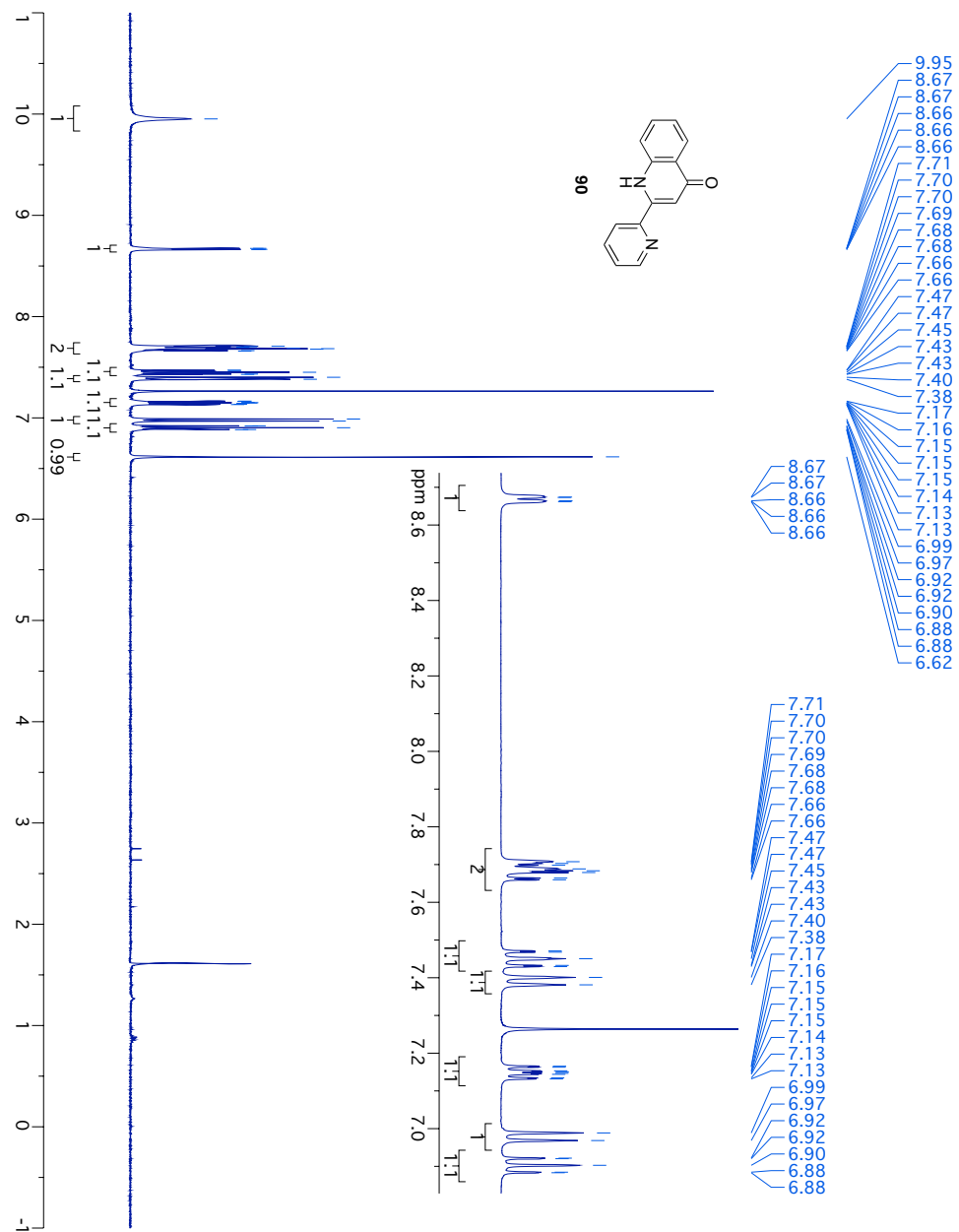
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1.47
1.45
1.43
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0.96
0.94

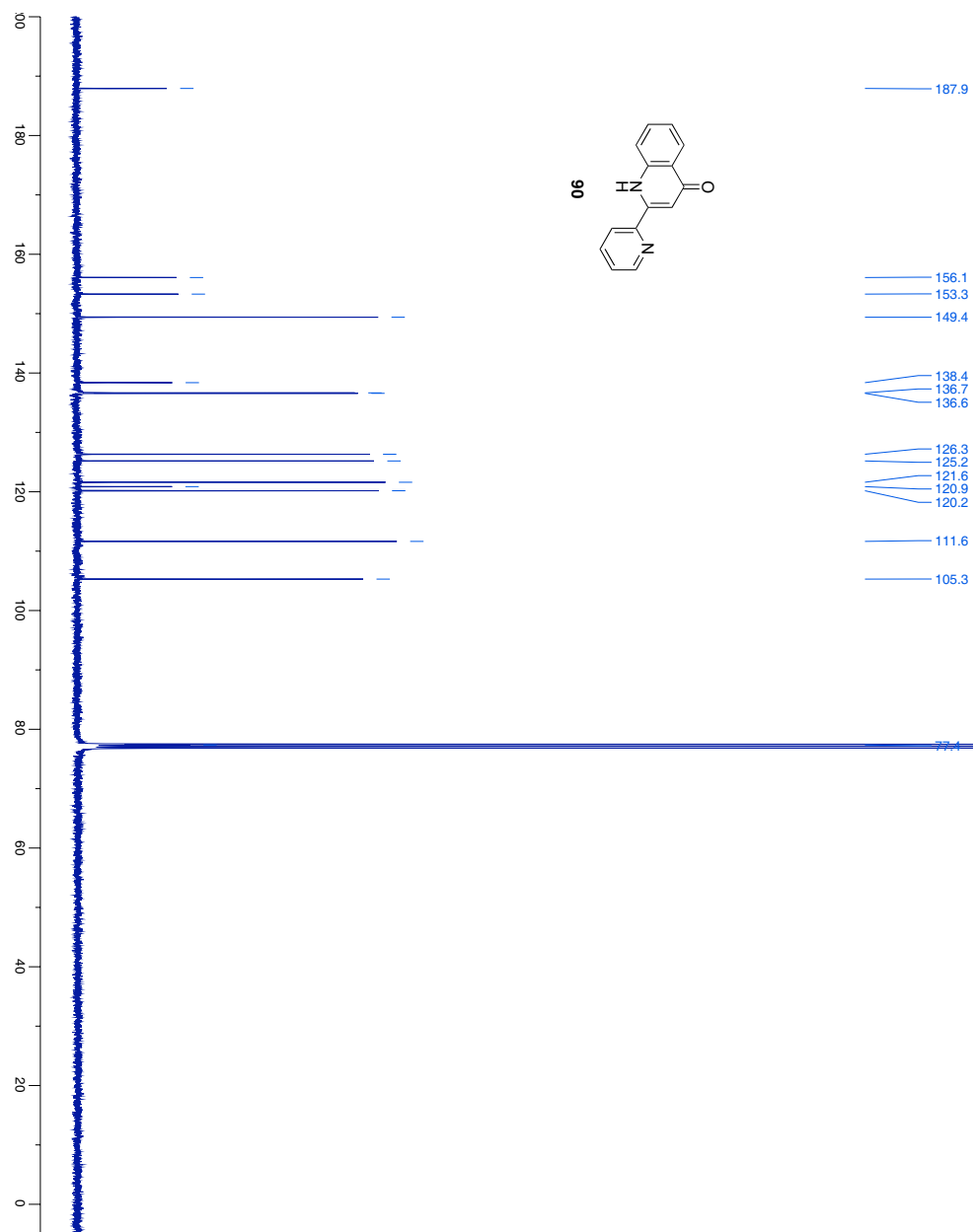


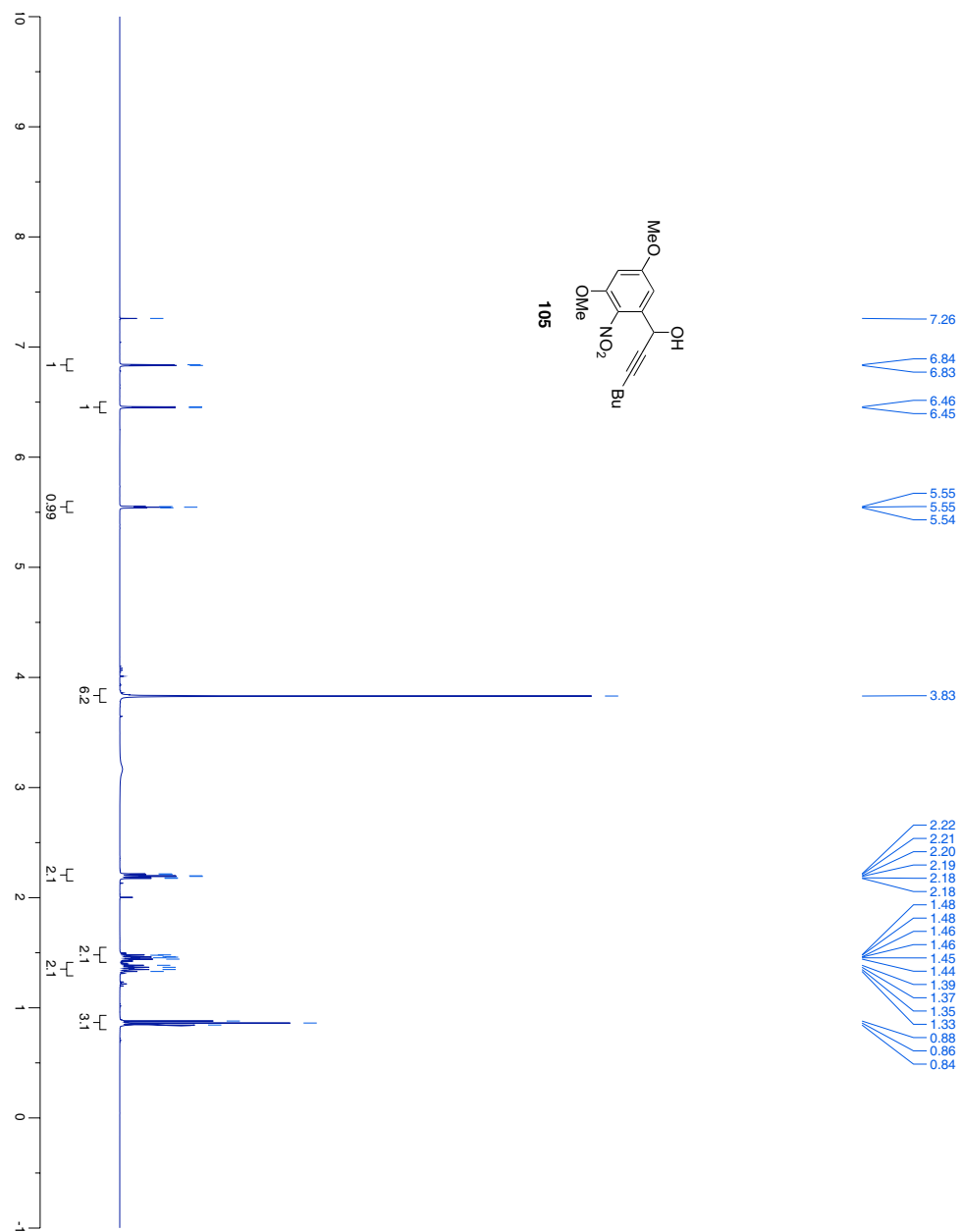


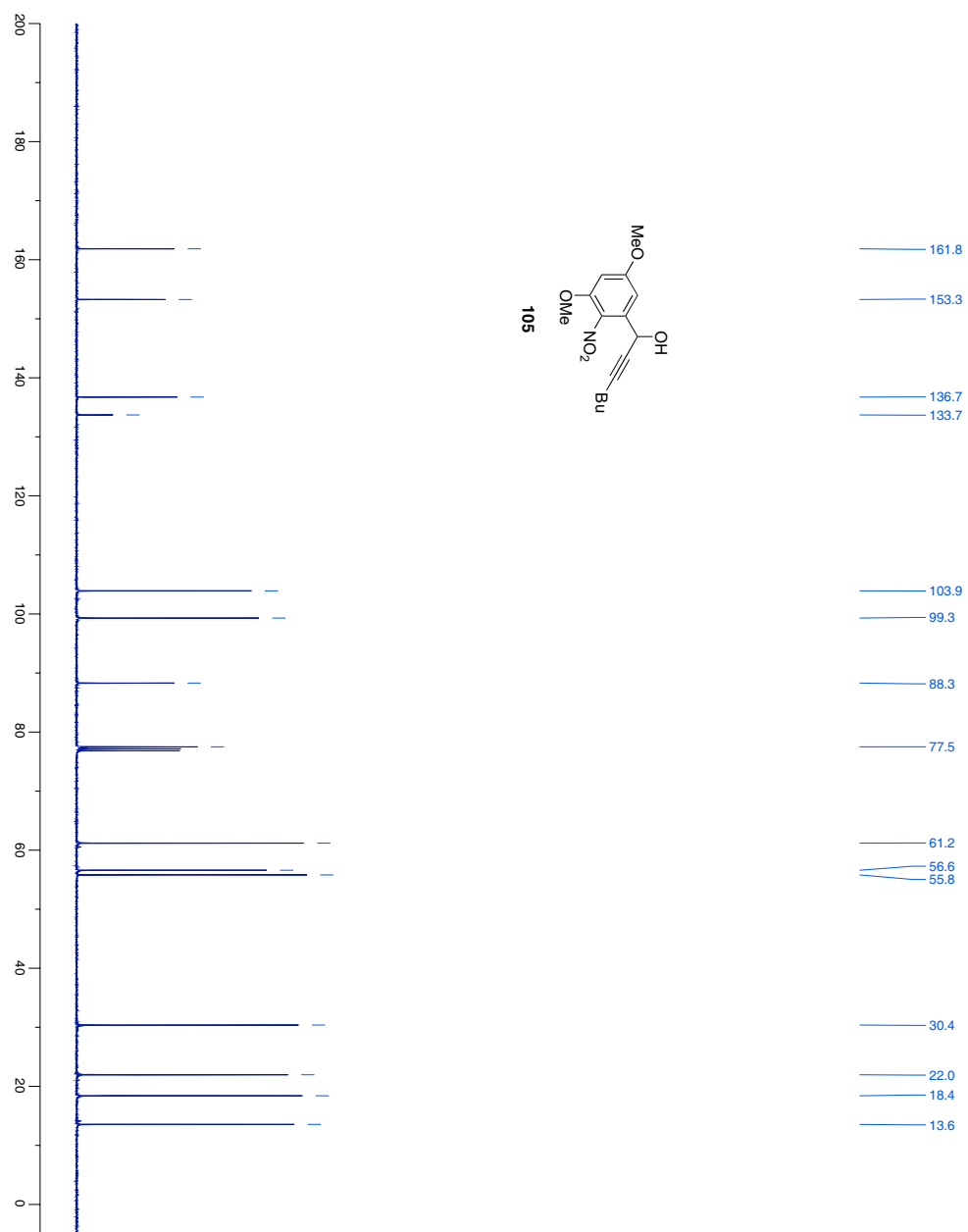


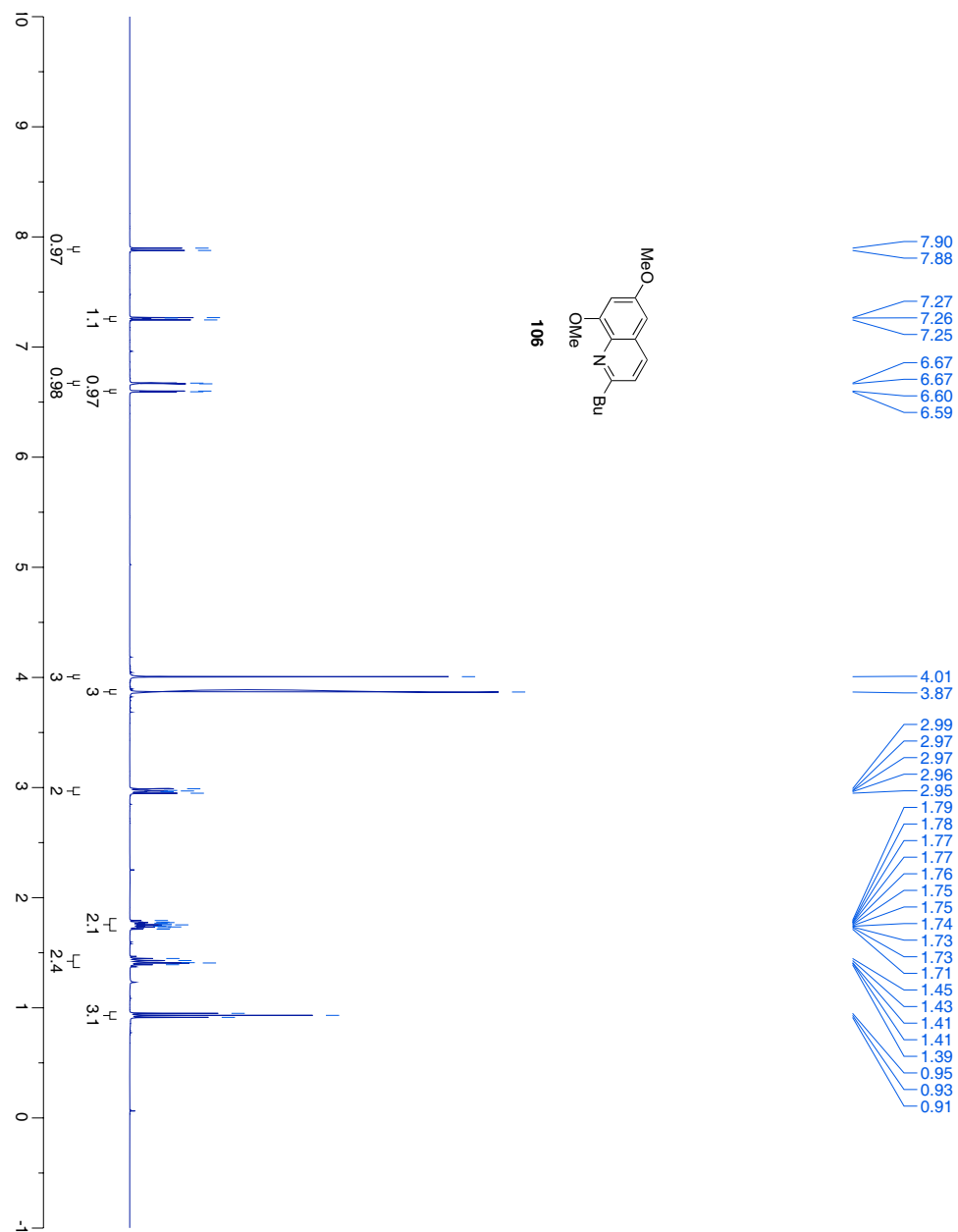


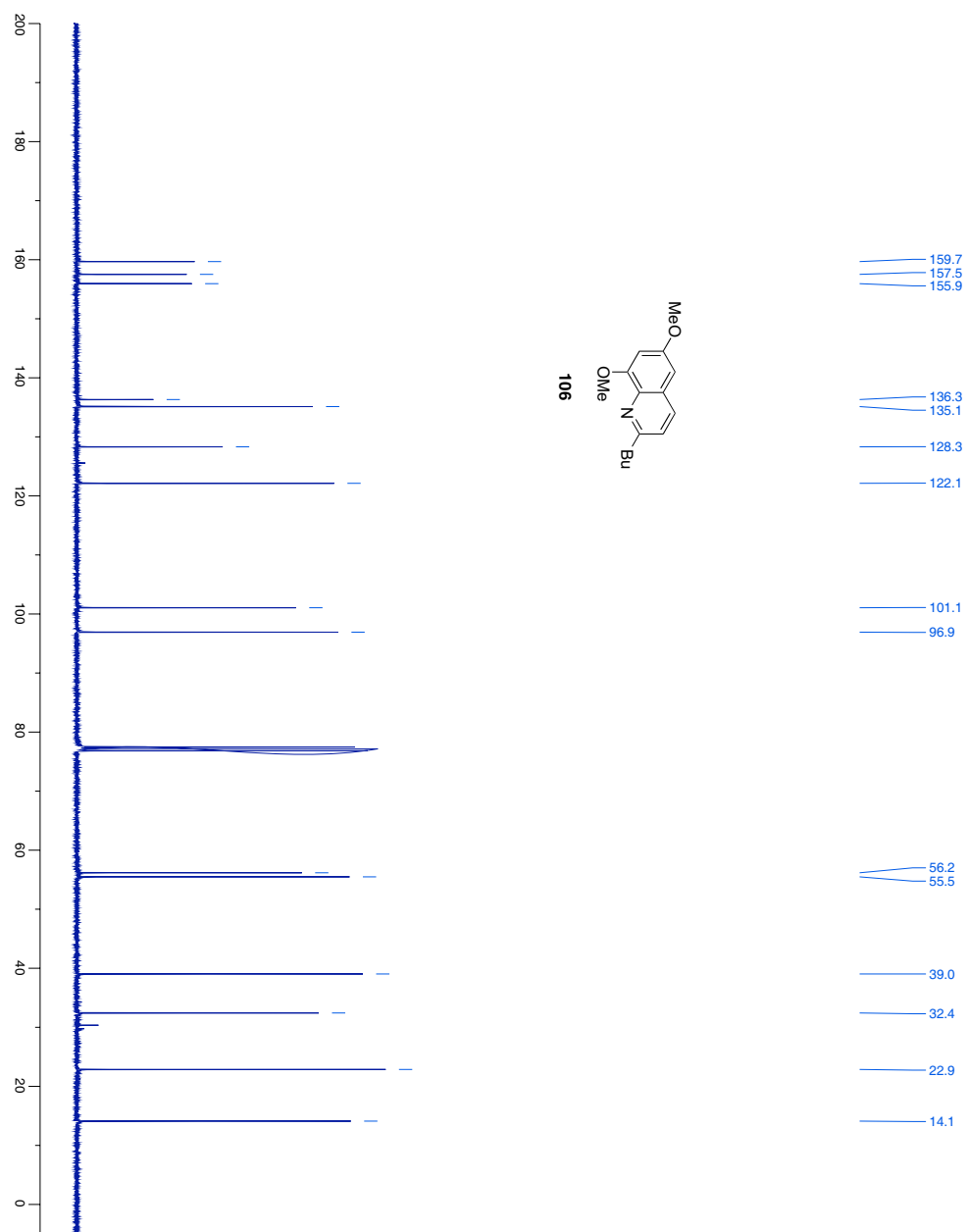


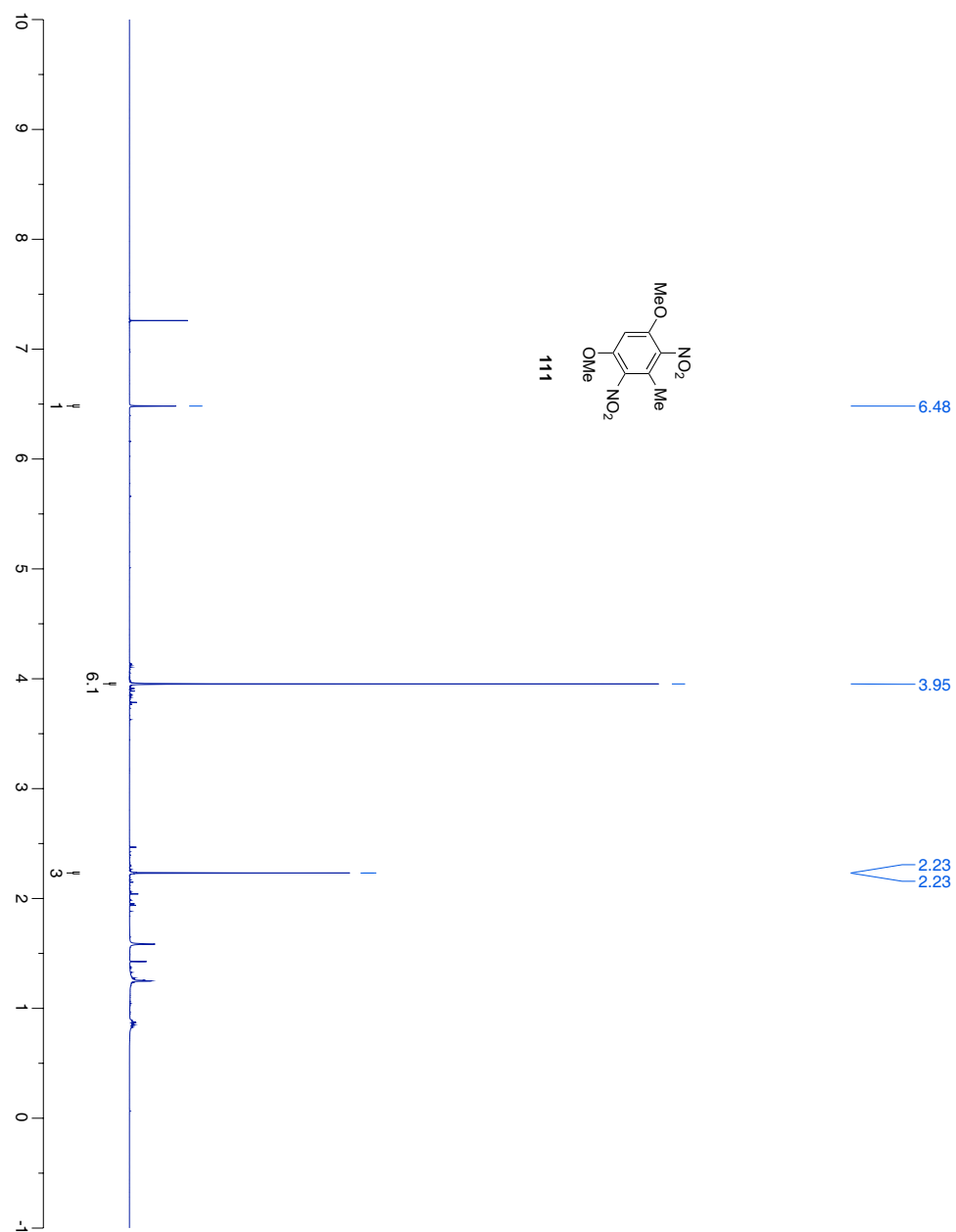


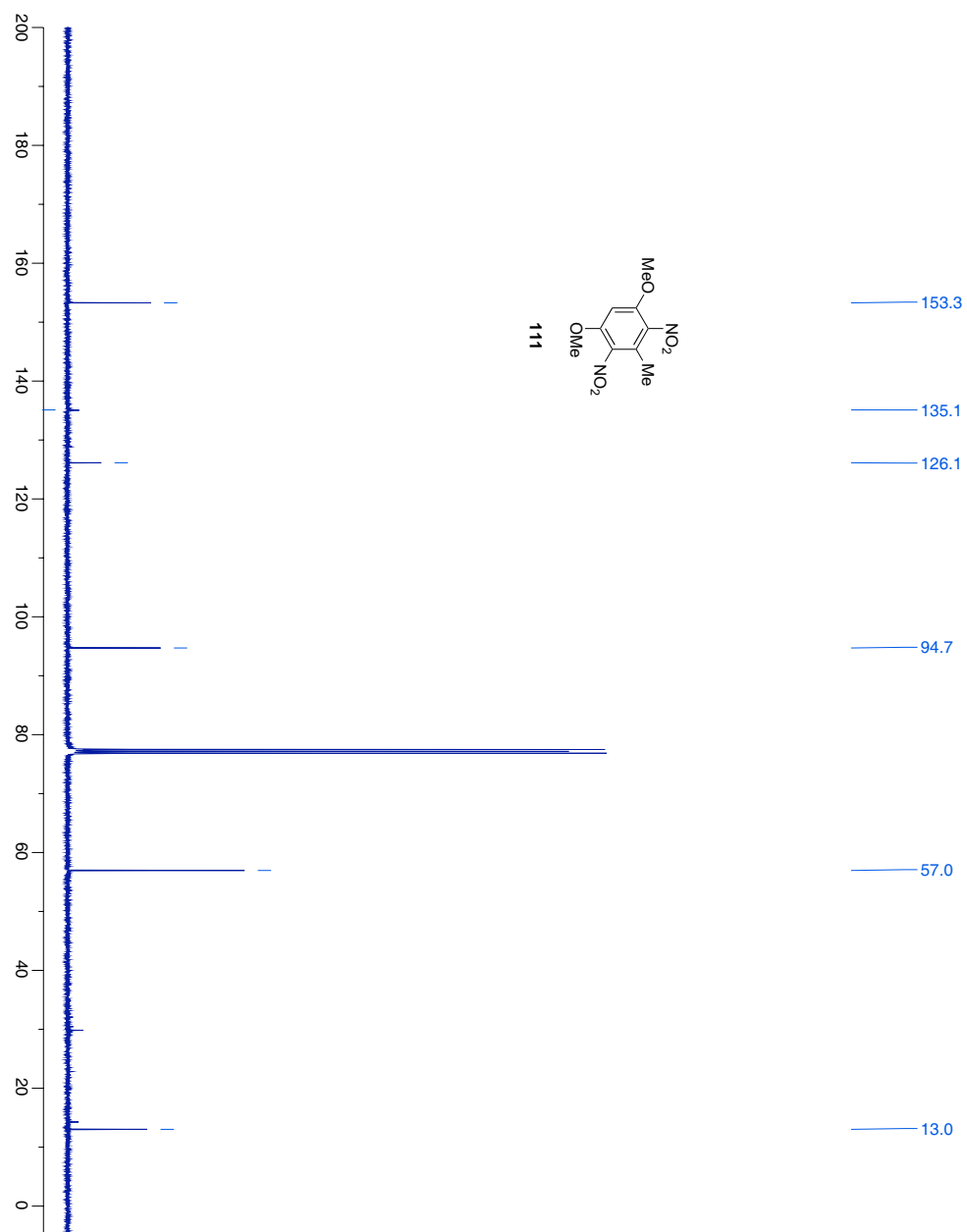


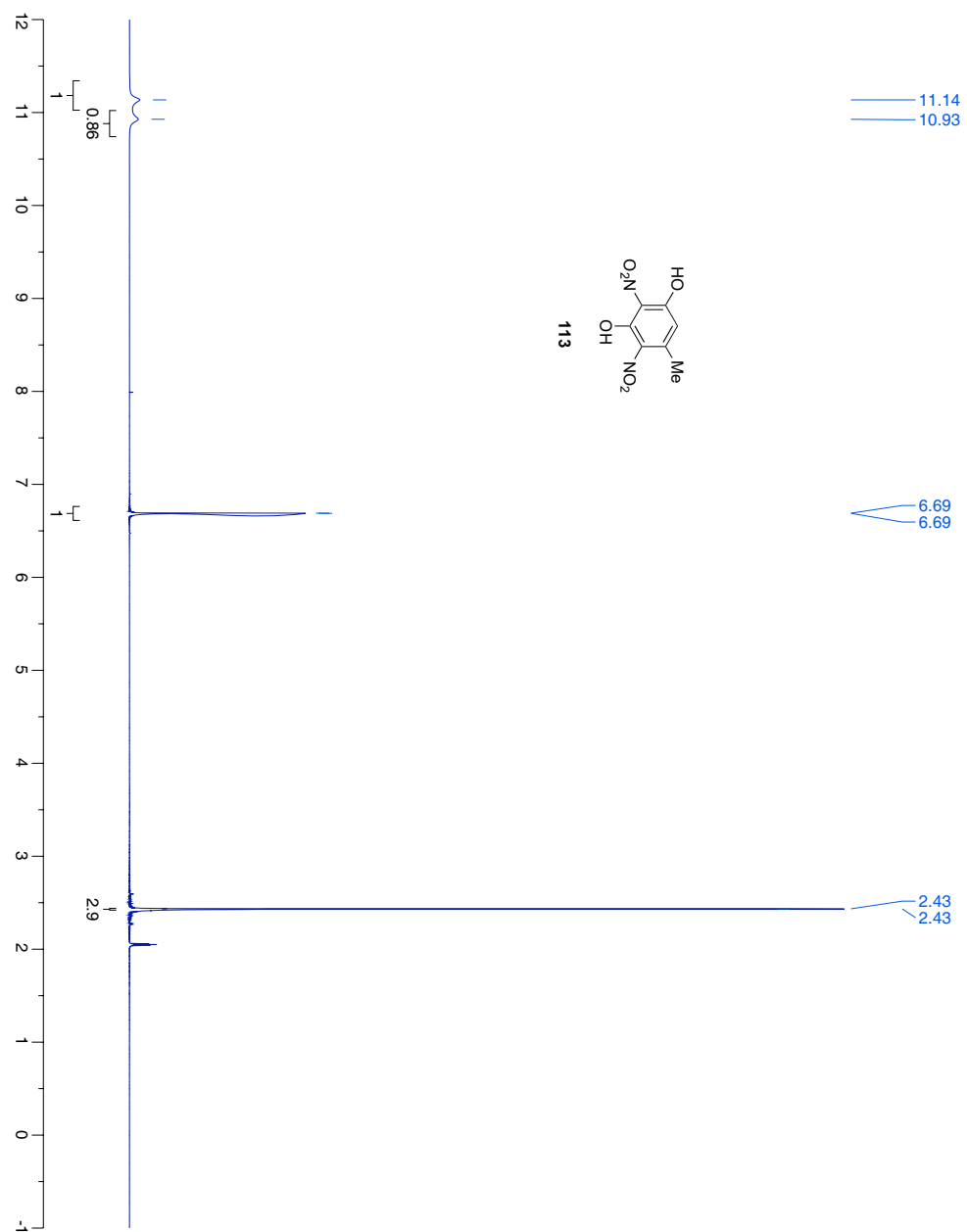


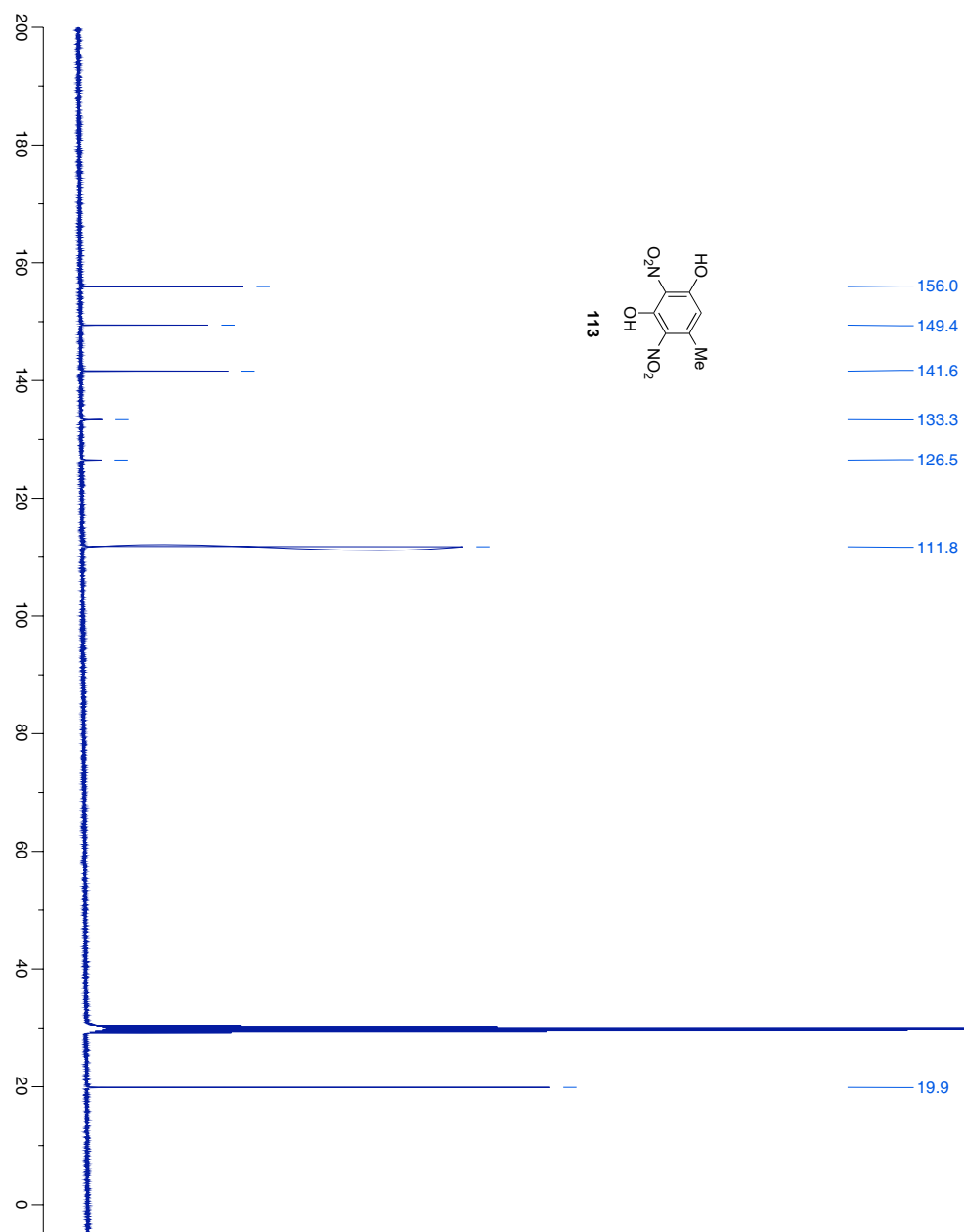


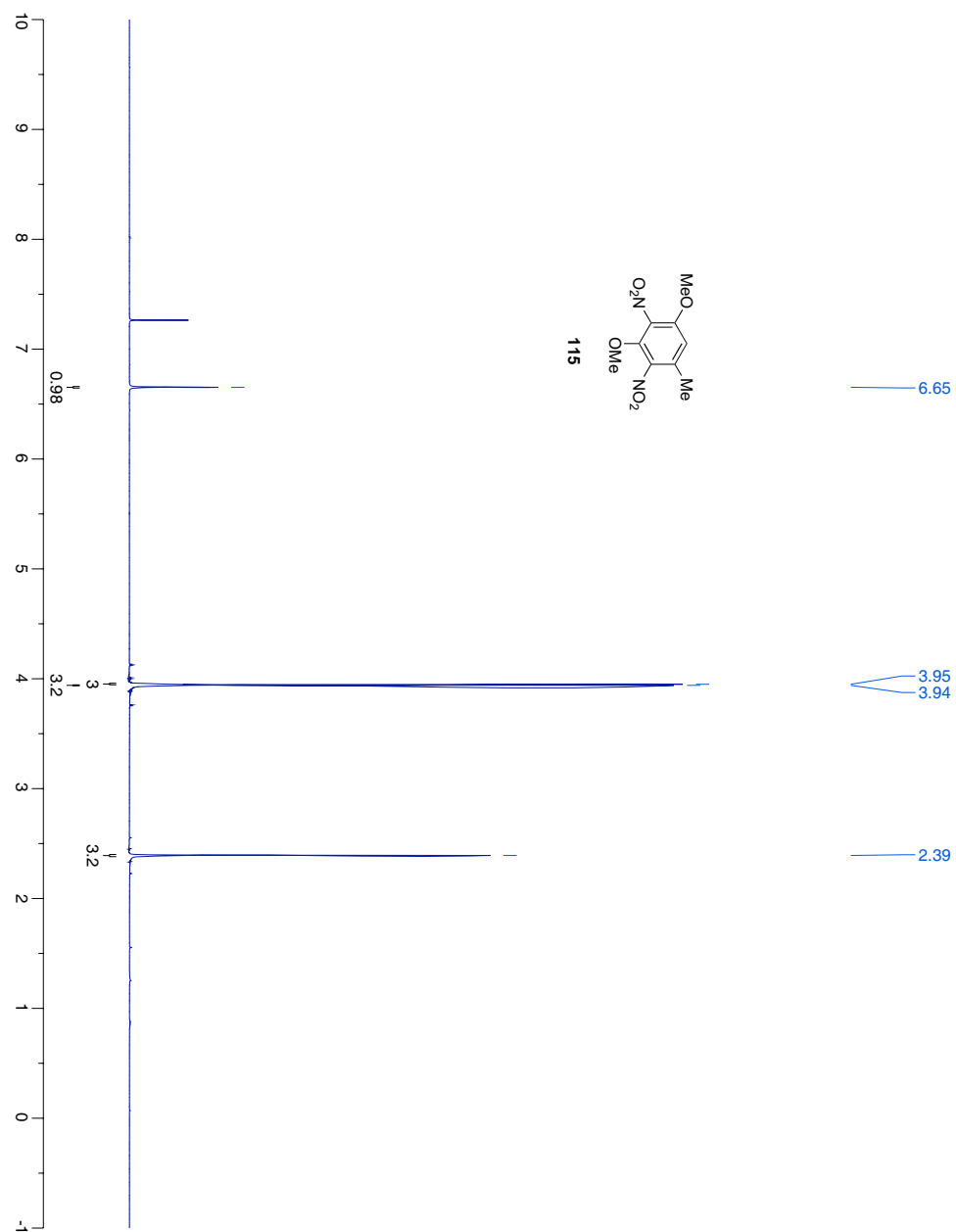


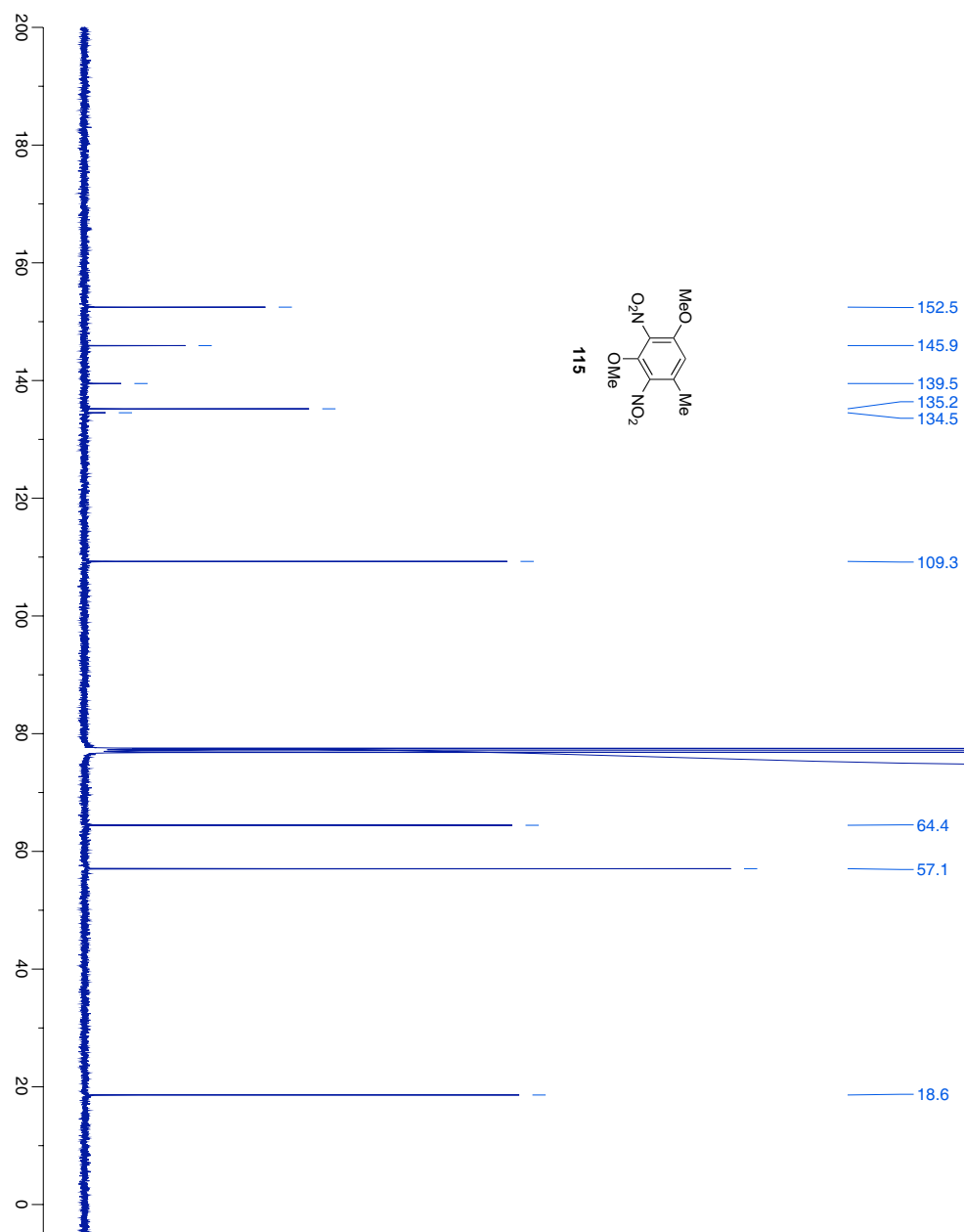


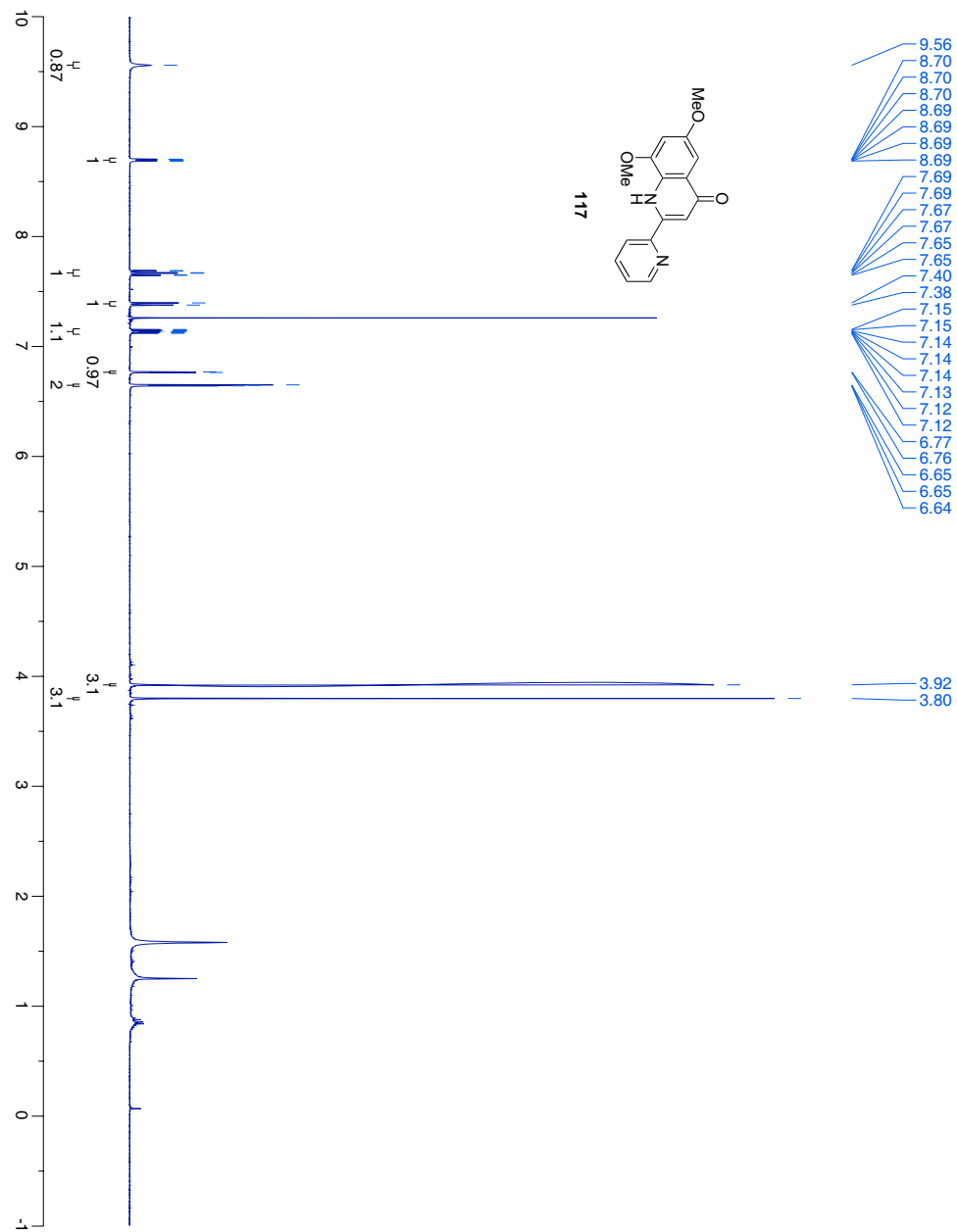


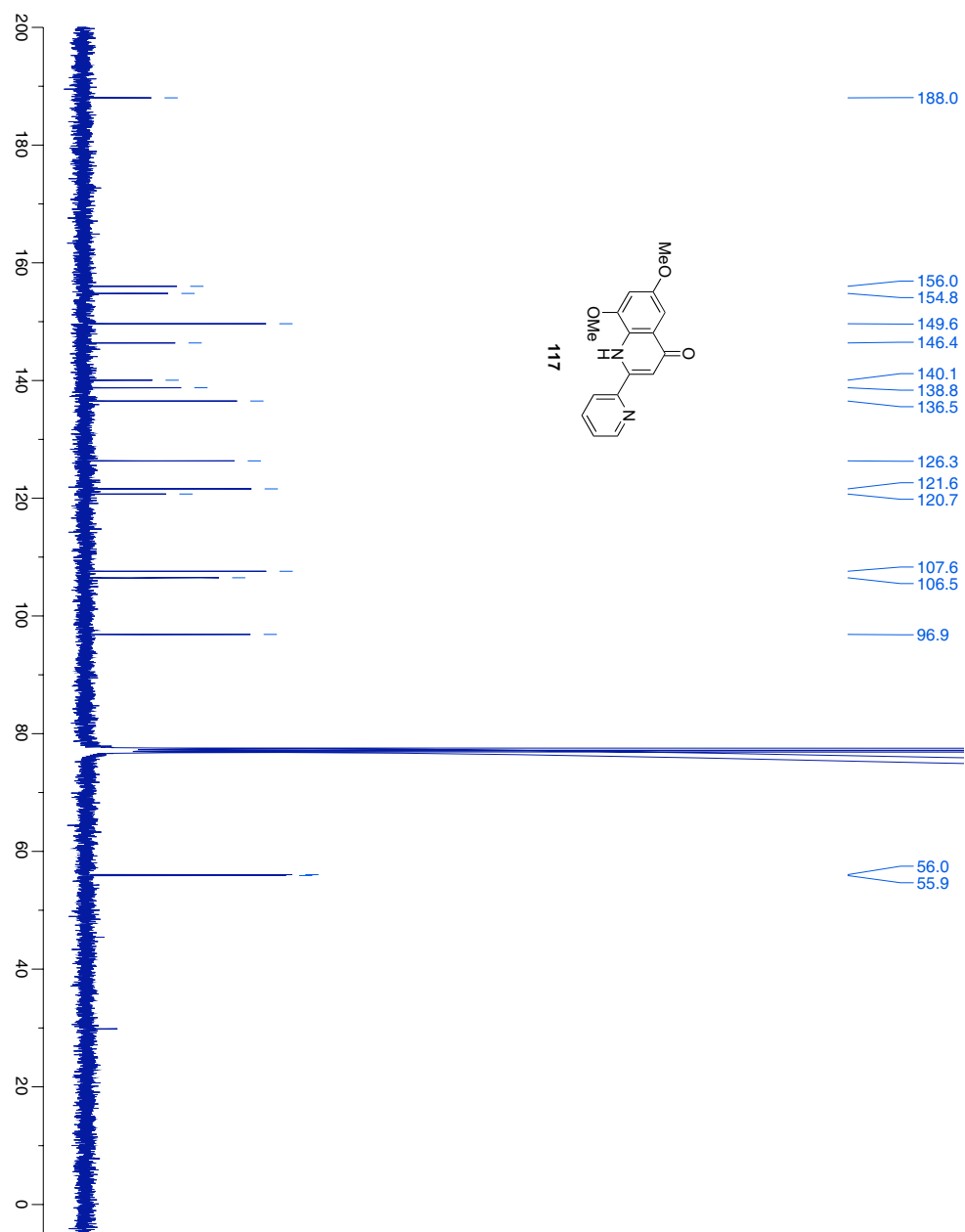












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